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October 10, 1975

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Research Advances

STEROID TREATMENT FOR SEVERE ASTHMA APPEARS SAFE DURING PREGNANCY

In an examination of the records of 55 asthmatic patients treated with steroids during pregnancy, the National Institute of Allergy and Infectious Diseases (NIAID) grantees found no evidence that such treatment resulted in increased risk for mother or child. On the basis of the information obtained in this study, the scientists consider the risk of fetal anoxia (insufficient oxygen) associated with severe asthma during pregnancy a greater potential hazard than the judicious use of corticosteroids.

These drugs (prednisone and prednisolone, principally) are often the only agents that will effectively control severe asthma, but pregnant animals treated with corticosteroids have been found to have an increased evidence of abortions, placental insufficiency, and congenital malformations in their offspring. Data on use of steroids in pregnant women have been conflicting.

In an attempt to define the problem further, NIAID grantees at Northwestern University Medical School, Chicago, and a colleague at the University of Washington Medical School, Seattle, collected data on 70 pregnancies in 55 patients: 14 from Northwestern; 18 from the University of Washington; and 23 from other medical centers. In this series the scientists found no maternal, fetal, or neonatal deaths. They did note slightly more premature births than would be expected in the general population. However, there was no increased incidence of toxemia, uterine hemorrhage, or congenital malformations.

Drs. Michael Schatz, Roy Patterson, John O'Rourke, and Howard Melam

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of Northwestern and Dr. Stanley Zeitz of the University of Washington reported their study in the *Journal of the American Medical Association*, August 18, 1975.

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Note to Subscribers:

The two Research Advances which follow are about recent findings in the study of juvenile diabetes.

Research Advances

MORE EVIDENCE IS FOUND OF ROLE OF GLUCAGON IN JUVENILE DIABETES

A California grantee of the National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD) has shown that suppression of glucagon secretion by somatostatin prevents the ketoacidosis associated with insulin deprivation in juvenile diabetics, providing further evidence of a role for glucagon in the development of this condition.

Evidence has been accumulating in recent years to indicate that glucagon may play a role in the development of diabetic ketoacidosis. For example, the present investigators recently reported that juvenile diabetics develop hyperglucagonemia in response to acute insulin deprivation, and that it is correlated with elevations in plasma glucose, beta-hydroxybutyrate, free fatty acid, and glycerol levels.

They now report that while mild ketoacidosis occurs ten hours after insulin withdrawal in such patients, suppression of glucagon secretion by somatostatin prevents development of ketoacidosis after insulin is withheld. Thus, insulin lack per se does not lead to fulminant diabetic ketoacidosis in humans, but glucagon excess apparently plays an essential part in the development of this condition.

Base-line blood specimens were obtained prior to terminating insulin infusions in seven insulin-dependent juvenile diabetics. Immediately thereafter somatostatin was infused for 18 hours while the patients were maintained in a fasting state. Control patients received a saline solution. Blood specimens collected periodically during the study periods were analyzed for changes in beta-hydroxybutyrate, glucose, alanine, free fatty acids, and

(more)

glycerol.

Somatostatin infusion prevented development of ketoacidosis for 18 hours after acute insulin withdrawal, while mild ketoacidosis occurred in control patients ten hours after insulin was stopped. Plasma beta-hydroxybutyrate, glucose, free fatty acid, and glycerol levels were all markedly lower during suppression of glucagon secretion by somatostatin, while plasma alanine levels were higher.

The investigators ruled out the possibility that these results were due to suppression of growth hormone secretion, and concluded that somatostatin acted primarily, if not exclusively, by inhibiting glucagon secretion. Because endogenous glucagon is gluconeogenic, lipolytic, and ketogenic in man, these actions of the hormone may play a substantial part in the development of human diabetic ketoacidosis.

NIAMDD grantee Peter H. Forsham, M.D., of the University of California, San Francisco, and associates reported their study in the *New England Journal of Medicine*, May 8, 1975.

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Research Advances

SPECIAL DIET PROGRAM MAY BE MORE EFFECTIVE FOR JUVENILE DIABETICS

A Boston grantee of the National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD) has shown that a diet restricted in cholesterol and saturated fat content, together with insulin control of blood glucose levels, is more effective than a conventional diabetic diet together with insulin control in reducing the incidence of hyperlipoproteinemia in children with juvenile diabetes.

The risk of life-threatening atherosclerosis is sufficiently great in the diabetic population that all efforts should be made to reduce any identifiable risk factors. Thus, the interrelationships between dietary cholesterol content, polyunsaturated-saturated (P/S) fat ratio, and degree of control of blood glucose levels have been studied in 270 juvenile diabetic children enrolled in two summer camps for diabetic boys and girls.

Results indicate that plasma lipids in juvenile diabetics were elevated upon admission to camp, with 24 percent demonstrating hyperlipoproteinemia. Proper control of blood glucose levels, together with a diet restricted in cholesterol and saturated fats, reduced the incidence of hyperlipoproteinemia significantly and more effectively than a conventional diabetic diet with simultaneous insulin control of blood glucose levels. It was concluded that a prudent diet, such as the one employed in this study, should supplement proper control of blood glucose levels.

Plasma lipids, blood glucose, and urinary glucose excretion were measured upon admission to and throughout the summer camping period. Groups of boys and girls were alternated on the usual diabetic camp diet (700 to 1,500

(more)

DIET (Cont'd)

mg cholesterol daily with a P/S ratio of 0.1) and the modified "prudent" diet (300 mg cholesterol daily with a P/S ratio of 1.0). Both diets supplied 40 percent of calories from fat, 40 percent from carbohydrate, and 20 percent from protein.

Elevated mean levels of cholesterol and triglycerides were almost evenly divided in children of both sexes upon admission to camp. Of the 24 percent with hyperlipoproteinemia, 11 percent had type II (markedly increased cholesterol) and 13 percent had types IV and V (markedly increased triglycerides). After following the usual camp diet, 21 percent were type II, 1 percent type IV, and none type V, with no reduction in overall incidence of hyperlipoproteinemia, despite lower triglyceride and glucose levels.

By contrast, after consumption of the modified "prudent" diet, hyperlipoproteinemia was reduced to 5 percent, with 4 percent type II and 1 percent type IV. The modified diet therefore produced a significant reduction in the overall frequency of hyperlipoproteinemia compared with the usual diet, particularly in the type II pattern.

NIAMDD grantee John S. Soeldner, M.D., of the Joslin Diabetes Foundation, and associates, reported their study in *Diabetes*, July, 1975.

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Research Advances

SPLEEN PLAYS BOTH SUPPRESSIVE AND PROTECTIVE ROLES IN QUARTAN MALARIA

The chronic nature of quartan malaria, a type of malaria characterized by fever every 72 hours, may be due to suppression of the body's defenses by the spleen, according to scientists at the National Institute of Allergy and Infectious Diseases and at the Southern Research Institute (SRI) in Birmingham, Alabama. They have found evidence of a possible deleterious effect of the spleen in the chronic stages of malaria in monkeys while confirming the spleen's protective role in the acute stages of the infection.

Among human malarias, the quartan form is the only one to result in infection that lasts many years if untreated. This chronic malaria often results in serious kidney disease. If scientists knew how the causative parasite, *Plasmodium malariae*, avoids the body's defenses for as long as 50 years, they might be able to develop a vaccine to strengthen these defenses. The need for a vaccine is obvious since malaria (in all its forms) remains a major cause of illness in Africa, Asia, and Latin America, despite extensive efforts to eradicate it over the past 20 years.

Scientists have known for many years that the spleen, a special lymph-node-like organ, plays some type of protective role in malaria. In an effort to determine the spleen's effect upon the body's defenses in quartan malaria, Drs. David J. Wyler and Louis H. Miller of NIAID's Laboratory of Parasitic Diseases collaborated with Dr. Leon H. Schmidt of SRI. They studied the course of infection of rhesus monkeys infected with *P. inui*, a monkey malaria parasite similar to *P. malariae*. One group of monkeys had

(more)

been splenectomized (spleens removed) prior to inoculation with the malaria parasite while another group had been splenectomized after infection. A third group consisted of animals whose spleens were not removed.

The researchers found that the spleen exerted its protective role during the acute stages of infection. Monkeys whose spleens were removed had 10 times as many parasites in their blood at the peak of infection as did the intact monkeys. Spleen removal did not affect the rate at which the parasites were cleared from the blood following this peak. Animals whose spleens were removed prior to inoculation exhibited a significantly higher mortality rate than did the intact monkeys or those whose spleens were removed after infection.

The monkeys with an intact spleen had persistent infection for as long as 15 years, although a few monkeys began to achieve self-cure after five years. In marked contrast, monkeys who had their spleens removed eliminated the infection within one year.

These observations clearly indicate that the function of the spleen in quartan malaria is more complex than previously appreciated. The investigators speculate that these opposing roles--protection and suppression--may possibly relate to the immunologic balance between the functions of two classes of lymphocytes--T and B cells--which are present in the spleen and lymph nodes.

If antibody (which is produced by B cells) is necessary for defense against the malaria parasites, while at the same time, the combination of antibody and parasite suppresses protective T cell function, then the outcome

(more)

of quartan malaria may depend on the interaction of these two effects. Further studies are needed to confirm or reject this hypothesis.

The scientists feel that such knowledge of the spleen's role in quartan malaria is essential if we are to understand protective immunity in malaria. They also hope that their findings will stimulate investigation into the function of the spleen in other infectious diseases.

These results were presented at the Fifteenth Interscience Conference on Antimicrobial Agents and Chemotherapy in Washington, D.C., on September 26, 1975.

#

SIDS--The sudden infant death syndrome (SIDS) is the leading cause of death in infants after the first month of life, claiming the lives of three infants for every thousand live births, according to the National Institutes of Health.

FOOD ALLERGIES--The most common food allergies are to fish, berries, nuts, eggs, cereals, milk, pork, chocolate, beans, and various fresh fruits. The National Institutes of Health reports that some people are also allergic to such substances as food additives.

#

Research Advances

TWO PANCREATIC CHOLERA PATIENTS RESPOND TO STREPTOZOTOCIN THERAPY

Scientists of the National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD) have reported a dramatic response to streptozotocin therapy in two patients with pancreatic cholera--an often fatal triad of diarrhea, hypokalemia and pancreatic carcinoma--that has been resistant to both medical and surgical treatment.

Pancreatic cholera is a syndrome of watery diarrhea and severe potassium deficiency (hypokalemia) associated with a non-beta islet-cell tumor of the pancreas. When the tumor is malignant and metastasizes, tumor resection, glucocorticoid therapy, and X-ray therapy may be beneficial. In almost half the cases, however, the patient dies of complications of diarrhea-induced hypokalemia within one year of diagnosis, and chemotherapy has been of little, if any, use.

The current research details a prompt and dramatic clinical response in two such patients who were treated with streptozotocin, an antitumor antibiotic that was administered via the hepatic artery. Whether streptozotocin therapy will induce remission in all such patients, and whether its beneficial effect will last for more than a year, remain to be seen.

Two patients with pancreatic cholera and islet-cell carcinoma--a 52-year-old white woman and a 54-year-old black woman--were referred to NIH. Their diarrhea and hypokalemia had persisted following resection of their tumors, which had metastasized to the liver, and they had failed to respond to conventional anti-diarrheal therapy. They were given streptozoticin (1.5 g

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per square meter body surface) at intervals of five to seven days.

Prior to such treatment, the patients had stool volumes ranging from two to eight liters per day and required 200 to 800 mEq/day of supplemental potassium and constant fluid replacement. After three to five doses of streptozotocin, both stool volume and number and size of hepatic metastases decreases markedly. One patient had normally formed stools for 12 months; the other had a 90 percent reduction in stool volume for 13 months with additional streptozotocin therapy. Both patients' serum potassium returned to normal without need for supplementation.

Pharmacologic studies suggested that administration of streptozotocin via the hepatic artery increased either tumor or hepatic extraction (or both) of this agent by two times, and decreased renal exposure to this nephrotoxic drug by one third. Numerous hormonal studies and measurements of jejunal adenylate cyclase and plasma vasoactive intestinal peptide, performed before and after such therapy, failed to elucidate the pathophysiology of the diarrhea.

C. Ronald Kahn, M.D., of the NIAMDD's Diabetes Branch and associates reported their findings in the *New England Journal of Medicine*, May 1, 1975.

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Photo Feature

WOMEN'S CHANGING ROLES ALTER THEIR CHILDBEARING DESIRES

Among the topics discussed at the October 7 Science Writers' Seminar on "Fertility and Women's Changing Roles" were women's participation in the labor force and fertility, socialization for fertility, and social pressures influencing family size. The seminar was planned by the Center for Population Research.

The Center for Population Research of the National Institute of Child Health and Human Development (NICHD) has the primary Federal responsibility for population research.

The research includes a comprehensive program of biomedical studies focusing on contraceptive development, fundamental biomedical research into reproductive processes, contraceptive evaluation, and diagnosis and treatment of infertility problems.

NICHD also supports and conducts a significant program in behavioral sciences,the goals of which include identification of the social, psychological, and economic determinants of fertility, and assessment of the consequences of population growth and change.

Motivation for use of contraceptives is as important as the availability of safe,acceptable contraceptive technology. The NICHD therefore supports biomedical research in an atmosphere in which changing social norms, patterns of behavior, and public need--in short, the context in which reproductive behavior occurs--are recognized.

There is ample evidence that women's changing roles alter their

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childbearing desires and their motivation to use contraception. Women's roles--and their perceptions of what constitute meaningful activities for themselves--are changing, as are their participation in the labor force, fertility expectations, and society's view of what an acceptable female role is.

Social changes include changes in the legal status of women; prohibition of pay discrimination; increases in educational and employment opportunities; and changes in abortion laws, divorce laws, and, if ratified, the equal rights amendment. What do these changes imply for fertility behavior? It should be emphasized that far-reaching changes are occurring rapidly in what was an essentially pronatalist society favoring an ideal family size of three or four children.

The pervasiveness of changes in fertility can be illustrated by the fact that the recent fertility decline has been shared by all the major United States ethnic groups, and that as shown by the 1970 fertility study, oral contraceptives are used at equal rates by all segments of American society, irrespective of religious belief. Evidence for other alterations in fertility and in the labor force participation of women in the United States was related to topics that were discussed at the recent NIH Science Writers' Seminar.

Between 1947 and 1972, the percentage of women aged 20 to 24 participating in the paid labor force rose from 44.9 percent to 55.6 percent; for women aged 25 to 34 years, from 32 to 47.6 percent; and for women aged 35 to 44 from 36 to 52 percent. The upward trend in female paid labor force partici-

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pation since World War II can be attributed almost entirely to a change in the employment status of married women. Today married women living with their husbands account for three-fifths of all female workers. Several factors are associated with the increase in paid employment for women, including the expansion of employment opportunities, and the decline in fertility rates. Declining fertility rates especially affect women in prime childbearing and childrearing years of 25 to 34 years of age.

As overall fertility has decreased since 1958, labor force participation has risen, especially during the late 60s and early 70s. When there are young children in the family, the likelihood of the mother working outside the home is reduced. However, labor participation of these mothers of very young children has risen steadily for a decade. The fact that participation of women with children under six years of age increased from 12 percent in 1950 to 30 percent in 1972 is especially noteworthy.

Since labor force participation is related to fertility, sociologists and demographers have often focused on it and are trying to determine what accounts for the observed relationship. These studies include the extent to which the timing of employment (prior to marriage, or prior to the first birth) is important; the influence of the contribution of the wife's salary to the family income; the influence of entry-reentry possibilities in the job market; and the influence and availability of day care, etc.

A crucial relationship between employment and fertility may be the correlation between fertility intentions and work intentions. Judith Blake

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Davis at the University of California, Berkeley, reported that high school girls who intended to work also intended to have fewer children than girls who did not plan to work, indicating that attitudes formed prior to employment and childbearing may be influential, as well as behavior during that period. Other studies indicate that girls who are socialized into less traditional roles recognize fewer differences between men and women in their abilities, and see women as able and competent. These girls are likely to be interested in working as well as having a family, and to want to limit their fertility.

In 1967, more than one-fourth of American women between the ages of 18 and 29 expected to have four children; by 1974, only one woman in 10 in this group expected to bear that many children. In 1974, 56 percent of wives between the ages of 18 and 24 thought they would have two children as compared with 37 percent in 1967. There has also been an increase in the percentage of wives expecting to bear no children, or only one child.

Among childless wives under 30 years of age, the two-child family is still favored by the majority; most childless women over 30 expect to have no children, but among the few who expect to have a family, a two-child family is favored. Increasingly, women are choosing roles which may exclude parenthood, thus challenging socialization over a lifetime.

Other NICHD-supported studies have identified psychological factors which contribute to high or low fertility. Some factors may result in social pressures on women to have more children than they might otherwise bear. Results show that existing norms imply that women should want and bear two to four children.

(more)

WOMEN (Cont'd)

Moments ago, this woman's role changed--at least temporarily--from her career to motherhood. The National Institute of Child Health and Human Development supports and conducts a significant program in behavioral sciences, the goals of which include identification of various determinants of fertility, and the assessment of the consequences of population growth and change. (NIH Photo #1468)

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NEWS & FEATURES From NIH

October 10, 1975

Photo Feature

TOPICAL DRUGS WILL BE TESTED AGAINST PSORIASIS

The National Institute of Arthritis, Metabolism, and Digestive Diseases has awarded a $132,000 contract to evaluate selected topical drugs for more effective psoriasis therapy. The coordinating center for the project is located at the University of Miami School of Medicine. Gerald D. Weinstein, M.D., Professor of Dermatology, will direct the program.

In association with William Eaglestein, M.D., and Jerry McCullough, Ph.D., approximately 30 drugs will be prepared as topical formulations. Many of the drugs were developed for systemic cancer therapy. Use of these agents for psoriasis by systemic administration has been generally successful, but carries with it a risk factor limiting use to the small percentage of all psoriatics with severe involvement.

The contract will provide for exploration of these drugs for administration topically on the basis that systemic toxicity might be better avoided by this route. Controlled studies of the selected compounds will be conducted at collaborating medical centers.

Psoriasis is a chronic skin disease of unknown cause that afflicts approximately two to four percent of the American population. It is characterized by silvery scales and underlying redness, and it generally occurs on elbows, knees, scalp and extensor surfaces. This disorder produces significant physical discomfort as well as social and psychological damage. One billion dollars annually is the estimated patient expense for frequently ineffective topical forms of medication.

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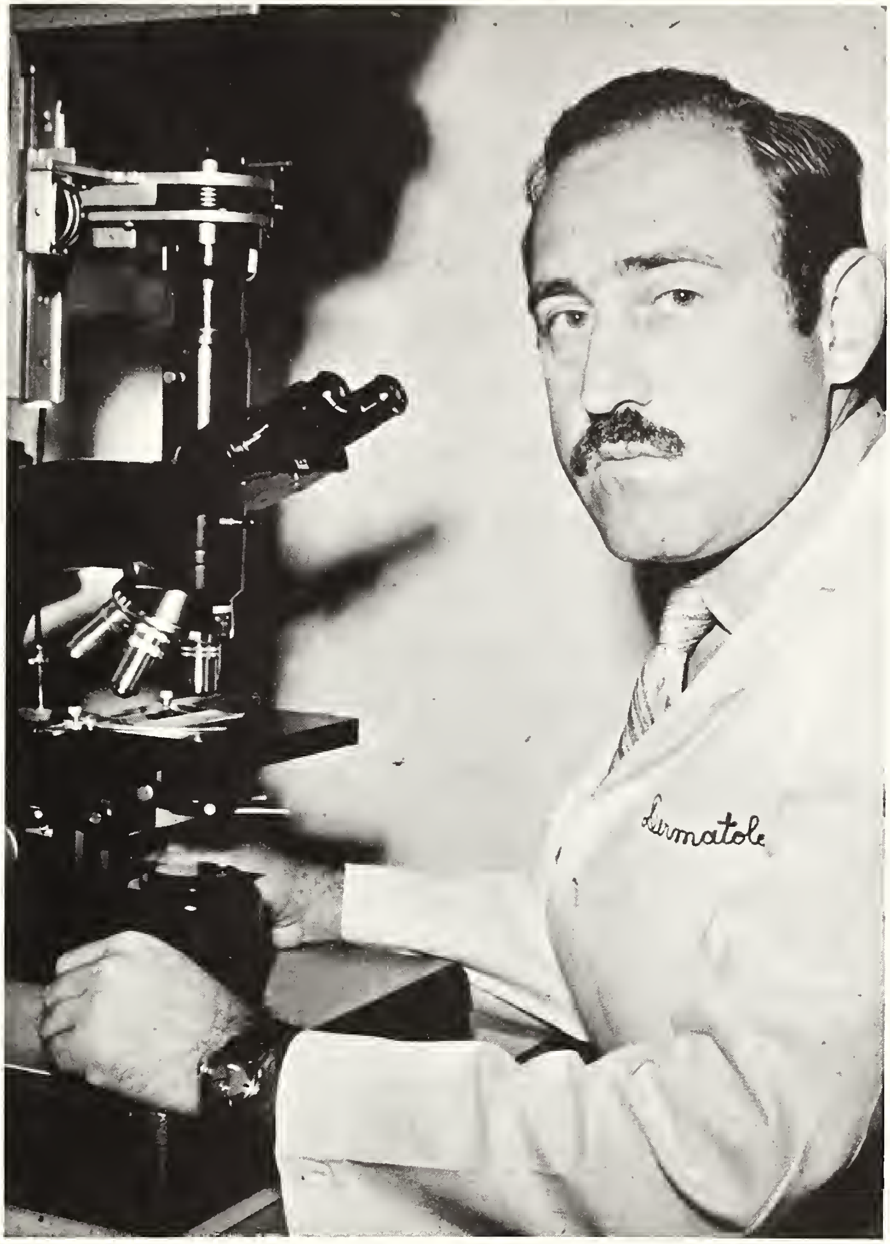

Gerald Weinstein, M.D., Professor of Dermatology at the University of Miami School of Medicine, is one of the pioneers in the development of topical therapy in psoriasis. While a Public Health Service officer at the National Institutes of Health, Dr. Weinstein participated in the development of systemic agents for the treatment of psoriasis, and has since then described the mechanisms for action of methotrexate on the epidermal cell cycle. Dr. Weinstein has recently been awarded a contract to screen other systemic agents for topical use in psoriasis. (NIH Photo #1469)

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Photo Feature

CONTINUING EDUCATION ON NEUROMUSCULAR DISORDERS IS PROVIDED ON VIDEOTAPES

A videotaped lecture series on neuromuscular disorders marks the entry of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) into televised, continuing medical education.

In less than three years NINCDS has succeeded not only in creating and producing a highly-popular series on neuromuscular disorders (many copies of the 28 currently available tapes are booked through mid-1976), but also in setting up a television studio that will enable the Institute to offer valuable medical educational material to physicians and scientists across the country--on free loan or low-cost purchase.

Originally, the series consisted of 17 lectures which were produced at a 1972 neuromuscular conference in Houston, Texas, using the local VA Hospital's TV studio. Since then, the course has added 11 more lectures, taped at a 1974 seminar in Houston and at the NINCDS studio.

Over 2,000 requests for the three-fourth-inch color tape cassettes have been received from 180 users since the program was announced to neurologists seven months ago. Users include individual physicians, medical school faculty, investigators affiliated with VA hospitals, and staff members of other medical institutions interested in keeping up-to-date on research developments in their specialized fields.

The Health Reports Section of the Office of Scientific and Health Reports is presently preparing five new lectures on neuromuscular disorders to supplement the original series, as well as a 14-tape series on multiple sclerosis which is based on a 1975 conference held at the National Institutes

(more)

VIDEOTAPES (Cont'd)

of Health. The multiple sclerosis tapes, which cover research on causes, epidemiology and treatments will be offered soon.

The NINCDS television studio was developed to meet the Section's need for an immediately-available low-cost television facility in which visiting research scientists can video-record their important medical research lectures, and make use of supporting visual materials. The studio, which became fully operational in September, is equipped with cameras, recorders, switchers, monitors, and special effects devices needed to produce, edit, and duplicate the continuing medical education lectures, as well as other sophisticated TV presentations on Institute research programs.

Much of the equipment is like that presently being adopted by network and other TV groups interested in making broadcast-quality programs at costs much lower than those which depend on traditional production techniques.

Bob Finney, head of the Health Reports Section, and staff members Lanny Newman and Gene Cowgill, add television production to their regular activities. Convinced that they have found a positive need, they are enthusiastically trying to develop scientifically up-to-date materials for the many medical and research centers that use specialized television courses to train their staffs.

Explaining their enthusiasm in developing and operating the TV facility largely on a part-time basis, Finney comments, "We feel that we are making an important contribution to continuing professional education in the neurological and communicative sciences, and we know that we are doing it at a fraction of what it would cost the Government if we were

(more)

VIDEOTAPES (Cont'd)

to use motion picture film or rented TV facilities."

Staff members of the NINCDS Office of Scientific and Health Reports welcome inquiries about their facilities and taped lectures. For more information write: Bob Finney, Building 31, Room 8A-06, NINCDS, National Institutes of Health, Bethesda, Maryland 20014, or call him at (301) 496-5751.

Bob Finney (left) checks microphone for Dr. Donald B. Tower, Institute Director. (NIH Photo #1470)

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Dr. Donald B. Tower (right), Director of the National Institute of Neurological and Communicative Disorders and Stroke, prepares to videotape an introduction to a series of tapes on multiple sclerosis designed for continuing medical education in the neurological sciences. Bob Finney, (left), Head of the Health Reports Section, Office of Scientific and Health Reports, advises Dr. Tower on presentation techniques. (NIH Photo # 1471)

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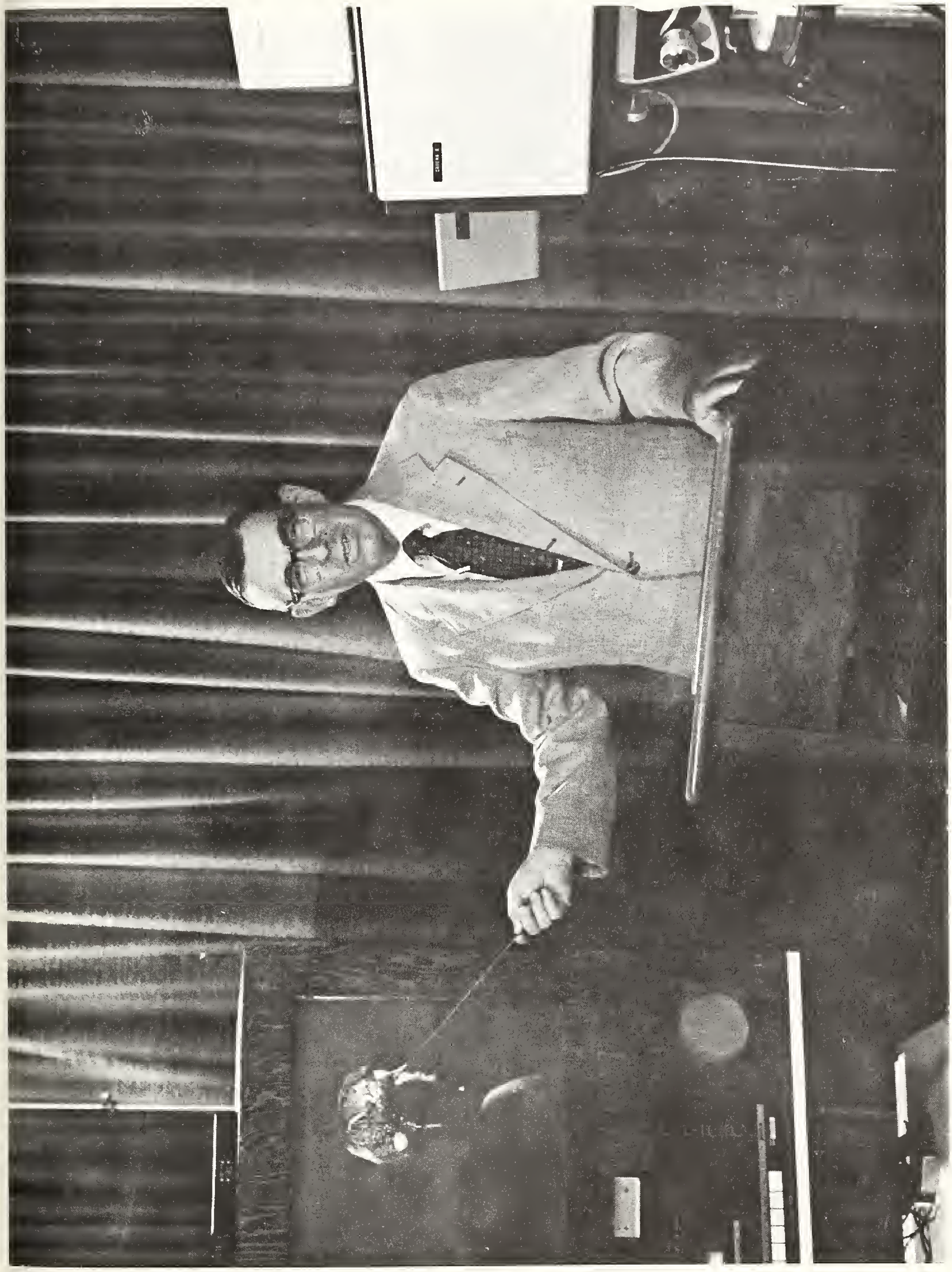

Dr. Donald B. Tower, Director of the National Institute of Neurological and Communicative Disorders and Stroke, rehearses an introduction to a videotaped lecture series on multiple sclerosis designed for continuing medical education. (NIH Photo # 1472)

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VIDEOTAPES (Cont'd)

Staff Members of the NINCDS Office of Scientific and Health Reports check lighting and equipment before a video taping session at the Institute's new television studio. The Institute already has produced a 28-tape lecture series on neuromuscular disorders, marking its entry into televised, continuing medical education. (NIH Photo # 1473)

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Research Illustrated

SCIENTISTS CHECK BLOOD CELLS, YOUNG MINDS, AND QUAIL EGGS

A medical student is shown carrying out a red cell osmotic fragility study in the Sickle Cell Disease Center at the University of Illinois Medical Center. The National Heart and Lung Institute provides grant support to several Sickle Cell Disease Centers. (NIH Photo #1474)

(more)

RESEARCH ILLUSTRATED (Cont'd)

A child's development of the motivation needed to master her environment is under study by scientists whose work is supported by the National Institute of Child Health and Human Development. (NIH Photo #1475)

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In one project, scientists at the National Institute of Environmental Health Sciences expose quail eggs to microwave radiation. This is done during studies to help determine the effect of microwave radiation on the developing embryo.
(NIH Photo #1476)

#

Disease Profile

CANCER OF THE BONE IS RELATIVELY RARE

Like other types of cancer, bone cancer is characterized by abnormal, uncontrolled growth which threatens life.

Malignant tumors, or cancers, always endanger life. They choke out normal tissue as they extend to adjacent tissue layers. They may also spread to other parts of the body. New growths thus related to the original tumor are called metastases.

Malignant tumors are divided into two main classes: Carcinomas, which develop in the lining and covering tissues of organs; and sarcomas, which develop in the connective and supportive tissues of the body. Most bone cancers are sarcomas; others are classified as lymphomas, cancers of the bone marrow and other blood-forming tissues.

Cancer of the bone is a relatively rare disease. Nevertheless, it is one of the more common types of cancer in children and young adults. It develops most frequently in young people 10 to 20 years old.

Any malignant tumor developing in the skeletal system is known as bone cancer. Most of the skeletal system is composed of bone itself, a highly specialized connective tissue which forms the rigid framework designed to bear body weight, provide fixed points for muscle action, and protect vital portions of the body. Other tissues, such as blood vessels, cartilage, and bone marrow, are associated with bone in the skeletal system and have other functions. Tumors may arise in these tissues also.

Malignant growths that originate in the skeletal tissues are called primary bone cancers. These include *osteogenic sarcomas*, which arise in the bone, cartilage, and fibrous tissues, *Ewing's sarcoma*, which usually arises in the center of the shaft, or marrow, of long bones and *plasma*

(more)

cell myelomas, which also arise in the bone marrow.

Secondary bone cancers are those that arise from primary tumors elsewhere in the body and reach the skeleton through the circulatory system or by extension from adjacent tissues. These are much more common than primary bone tumors. The most common sources of the metastases are cancers of the breasts, kidneys, thyroid, and prostate gland. Ordinarily these cancers occur in middle-aged and older persons.

There are many types of benign bone tumors. A few of these may develop into bone cancer. *Chondromas* (cartilage tissue tumors) often develop into cancer, but benign giant cell tumors of the bone seldom develop into cancer. A physician usually treats these with surgery or radiation as a preventive measure. *Paget's disease* of the bone is a common condition that sometimes precedes the development of bone cancer.

A common symptom of bone cancer is pain, which sometimes seems to be relieved by exercise, but at other times is aggravated by motion. The pain may not be constant, but may seem to come and go.

Although pain may develop in any area of the skeleton, the predominant sites are the region of the knee, thigh, arm (especially the upper part), ribs, and pelvis.

Other symptoms include swelling and fever. Depending on the type of bone tumor, swelling may precede or follow pain. Fever is not usually present when the tumors are small.

Since the symptoms of bone cancer and benign conditions are similar, the physician suspecting cancer looks for further clues in a thorough physical examination of the patient, including laboratory tests of the blood

(more)

and urine, and X-ray pictures.

To establish a true diagnosis usually requires a team effort by the patient's physician, radiologists, bone pathologists,and orthopedic surgeons.

Bone cancers usually are treated by surgery, but there is increasing evidence that combined modality treatment, using surgery, radiotherapy, and combinations of chemicals is producing greatly improved long-term survivals in many cases. One of the most important things a patient can do is to seek a competent physician and have followup examinations every few months for several years after treatment.

Many theories attempt to explain the cause of bone cancer, but none has been proved conclusively. One of the most popular is the theory that injury causes bone cancer. Although many times a blow or a fall immediately precedes the discovery of cancer, it is likely that the accident only calls attention to a tumor that was present beforehand. Increased production by the body of a growth factor, as yet undefined, has been suggested as a possible cause of osteogenic sarcoma and Ewing's sarcoma in adolescents, since these types of bone cancer seem to occur often in young people of taller-than-average stature.

A procedure called isotope scanning may be employed if bone cancer is suspected. With this method, radioactive isotopes are injected into the patient whose body is scanned with an instrument similar to a Geiger counter. Since several radioactive isotopes tend to be incorporated chiefly in malignant bone tissue, areas of bone that emit high levels of radioactivity often indicate the location of a hidden tumor. These and other investigations of the nature and causes of bone cancer will contribute to our knowledge,and should eventually lead to more effective ways of preventing or controlling these cancers.

#

News Releases Issued

TEACHING METHODS--Regulations to implement the National Cancer Institute's new Clinical Cancer Education Program have been published in the *Federal Register*.

The program is designed to stimulate development of innovative teaching methods in cancer prevention, diagnosis, treatment, and rehabilitation.

Proposed regulations appeared in the *Federal Register* on March 24, 1975, to allow public comment. The final regulations are substantially unchanged from those proposed.

National Cancer Institute grants to fund undergraduate and graduate cancer education activities over and above existing curricula will be available for schools of medicine, dentistry, osteopathy, public health, and affiliated teaching hospitals and cancer institutions in the 50 States, the District of Columbia, and American commonwealth and trust territories. Only nonprofit institutions are eligible.

"Education of physicians and dentists in the management of cancer is an important part of the National Cancer Program," said Dr. Frank J. Rauscher, Jr., Director of the National Cancer Program, National Cancer Institute, when announcing the proposed regulations.

"It is essential to improve instruction in cancer-related subjects at both graduate and undergraduate levels. The new education program will coordinate activities of faculty from many departments to provide carefully designed, multidisciplinary cancer instruction."

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Editors of publications may request a glossy print of the numbered photographs that appear in this issue.

NEWS & FEATURES From NIH
National Institutes of Health
Building 31, Room 2B-10
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NATIONAL INSTITUTES OF HEALTH

October 25, 1975

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NIH News Branch
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Research Advances

SCIENTISTS RECOMMEND DROPPING DYE-LIGHT TREATMENT OF HERPES INFECTIONS

In a placebo-controlled study of patients with recurrent herpes infections, National Institutes of Health grantee scientists found the dye-light treatment ineffective either in promoting healing or in preventing recurrences of "cold sores" or genital infections.

Herpes simplex virus (HSV) infections usually heal, in time, without treatment, but they frequently recur and are generally of sufficient discomfort and embarrassment to cause many patients to seek some form of therapy. One new treatment method, based on *in vitro* investigations, animal studies, and some circumstantial evidence, is photodynamic inactivation of the virus. This is achieved by treating the herpes lesions with a dye, such as neutral red, and then exposing the lesions to light. However, it has been shown that photodynamically inactivated HSV can induce cancerous changes in cells *in vitro*, suggesting that this form of treatment is not without hazard.

The present study was set up by medical personnel at Beth Israel Hospital, Children's Hospital Medical Center, and Harvard Medical School, all in Boston, to evaluate, in a controlled manner, the effect of photodynamic inactivation upon recurrent HSV infections.

The 96 patients entered in the study were all volunteers who sought treatment for recurrent cutaneous or mucocutaneous HSV infections. Most patients were employees or students at local nursing schools and universities.

During the course of the study, herpes lesions in 87 of 170 episodes of infection were treated with a solution of neutral red dye before being

(more)

exposed to a 100 watt white incandescent lamp for 15 minutes. Patients were instructed to repeat the light exposure after four to six hours and then again at 24 hours. If new eruptions appeared within 48 hours, they were similarly treated.

In the remaining 83 episodes of infection, the herpes vesicles were treated with a placebo, the chemical phenosulfonphthalein, and subsequently exposed to light as described above.

Patients were asked to return for questioning and examination every third day until healing was complete. They were also asked to return if they had any recurrences. Healing times were computed to the nearest day at which discomfort ceased, crusting occurred, and the lesions were entirely healed. The effect of treatment on recurrence was evaluated by determining the interval in weeks between initiation of treatment and the next outbreak of vesicles. Recurrent lesions were classified as being at the same site, in the same general area, or at a remote site.

The neutral dye and the placebo-treated patients did not differ significantly in the duration of their discomfort or in the time to crusting or complete healing of their lesions. For all patients, pain ended on about the fifth day and healing was complete on about the seventh.

Furthermore, treatment with the neutral red dye did not demonstrably affect the frequency of or length of interval between subsequent recurrences of herpes infections. Differences between recurrences at the same site following red dye or placebo treatment (16.9 weeks versus 21.1 weeks) were

(more)

not considered statistically significant. The intervals between recurrences at sites other than the original one were almost the same for the two chemicals used in treatment (20.1 weeks for red dye; 21.9 for phenosulfonphthalein).

Since this placebo-controlled clinical study failed to demonstrate the efficacy of neutral red dye and light in the treatment of recurrent HSV infections and since a potential carcinogenic risk in involved, the scientists recommend that routine use of this form of therapy be discontinued.

The study was carried out by Drs. Martin G. Myers, Michael N. Oxman, and Kenneth A. Ardt, and by Joan E. Clark, R.N. Results were reported by Dr. Myers at a Symposium on Antivirals with Clinical Potential, sponsored by the National Institute of Allergy and Infectious Diseases and held at Stanford University, Palo Alto, California, August 26 to 29, 1975.

#

Research Advances

SPECIAL ANESTHETIC MANAGEMENT IS NEEDED FOR SICKLE CELL PATIENTS

Anesthetic management of the patient with sickle cell disease calls for close attention to basic sound practices, according to Henry L. Price, M.D., professor and chairman of the Anesthesiology Department at Hahneman Medical College and Hospital of Philadelphia.

Difficulties often encountered are chronic anemia, a subnormal lung function, and enlarged heart and impaired liver and kidney function, he said.

"The immediate post-operative period is a critical one for the sickle cell patient," Dr. Price said in a lecture at the refresher course program of the American Society of Anesthesiologists annual meeting in Chicago in October 1975. "Incisional pain, the use of potent depressant drugs and muscle relaxants,and the reduction in arterial oxygen tension that normally persists into the post-operative patient imperil the sickle cell patient. Depending on the operative site, the arterial oxygen tension may not return to pre-operative levels for days."

The incidence of sickle cell disease among the black population is about one percent. Sickle cell disease is an inherited disorder in which the red blood cells contain abnormal hemoglobin. Individuals with both abnormal and normal hemoglobin in the red blood cells are said to have the sickle cell trait. About 8.5 percent of the black population have the trait. They usually have the prospect of a normal life span.

The research is supported in part by the National Heart and Lung Institute.

#

Research Advances

TRACE ANESTHETIC GAS LEVELS REMAIN OPERATING ROOM PROBLEM

A sampling of the air in hospital operating rooms and dental operating rooms in 98 institutions showed trace anesthetic gas levels averaging significantly higher than the proposed federal standards for allowable levels, according to a report to the annual meeting of the American Society of Anesthesiologists in Chicago in October 1975.

The average for the 98 institutions corresponds to the measurements obtained in two previous reports from single institutions. Traces of spilled anesthetic gases have been linked with a higher incidence of spontaneous abortion and congenital malformation in offspring of personnel in the operating room than similar groups working elsewhere in the hospital.

Sampling levels in small community hospitals, John H. Lecky, M.D., assistant professor of anesthesia, University of Pennsylvania, Philadelphia, found trace levels of gases varied from institution to institution, reflecting the inflow rates and concentration of gas, the effectiveness of ventilation system, and the equipment used to scavenge the spilled gases.

Nitrous oxide levels ranged from zero to 1281 parts per million, halothane from zero to 199 parts per million, and enflurane from zero to 234 parts per million. The average levels for the three gases were 177, 11.7, and 9.8, respectively. These values agreed with levels obtained in the earlier single institution studies of unscavenged operating rooms and were significantly greater than proposed standards of 30 parts per million for nitrous oxide and one-half part per million for halothane.

In samples obtained from operating rooms where scavenging equipment

(more)

was used, the average levels were close to the proposed standards.

"The levels of anesthetic wastes seen in dental operatories suggest that the dentist, using high flows and non-breathing techniques, appears to have the most serious contamination problem with nitrous oxide levels ranging from 94 to 3,000 parts per million, averaging 793," said Dr. Lecky. The research project was funded in part by a National Institute of General Medical Sciences grant. Various studies are being conducted in an effort to reduce exposure to harmful levels of trace anesthetic gas.

#

EMPHYSEMA--Life expectancy is reduced by circulatory complications combined with emphysema. Especially serious are such added problems as right-heart "overwork" owing to high blood pressure in the pulmonary blood vessels and an abnormal increase in the number of red blood cells, according to the National Institutes of Health.

#

Research Advances

POSSIBLE INTERACTION OF MEDICATION, SURGICAL ANESTHETICS IS IMPORTANT

Anesthesiologists must know what medications patients are taking for their various ailments in order to avoid potential hazards when they are anesthetized for surgery.

Harry Wollman, M.D., chairman of the department of anesthesia at the University of Pennsylvania, said the risk of discontinuing the medication for a period of time must be weighed against the risk of interaction with the anesthetic.

Drugs in widespread use today include a number of newer compounds for high blood pressure, various compounds for depression, L-dopa for Parkinsonism,and a class called beta adrenergic blocking agents used for a variety of reasons, including arrhythmias, angina, and high blood pressure. These are among the drugs to which anesthesiologists pay special attention.

"A number of years ago, some anesthesiologists recommended withdrawing reserpine for two weeks," Dr. Wollman said in his scheduled talk at the annual meeting of the American Society of Anesthesiologists, in Chicago in October 1975. "Later it became clear that hypertension out of control was more dangerous than hypertension under good control, and reserpine was continued until the day before or the day of surgery. In today's practice this lesson is remembered,and patients being treated for hypertension have their medication continued until six, 16, or 24 hours before surgery. This is generally true with most antihypertensive drugs."

L-dopa is converted into dopamine, a compound deficient in the nervous

(more)

system of patients with Parkinson's disease. If dopamine should accumulate in areas other than the central nervous system, the theoretical hazards of abnormal heart rhythm, low blood pressure, and high blood pressure are of concern during anesthesia.

"The most informed thinking today is that the drug should be continued until six to 12 hours before operation," said Dr. Wollman.

The theoretical risk in patients using the beta adrenergic blockers is low blood pressure and heart failure. "The most extreme view is that patients should be withdrawn for two weeks prior to surgery," Dr. Wollman said. "Others ask how this can be done if the drug is truly indicated; in the control of arrhythmias, for example. Recent reports point to the dangers of sudden withdrawal from B-blockers. The most common practice is to continue the drugs until six to 24 hours before surgery." The research is supported in part by the National Institute of General Medical Sciences.

#

Research Advances

SUBDURAL HEMATOMA MIGHT BE TWICE AS COMMON AS REPORTED

A Minnesota grantee of the National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD) has obtained evidence to indicate that subdural hematoma (effusion of the blood occurring in layers) is perhaps twice as common as reported in patients undergoing chronic hemodialysis. He has compared his study of 13 patients with literature reports about nine others.

Since 1969 only nine patients have been reported in the literature as having developed subdural hematoma while receiving regular hemodialysis. The present report details this condition in 13 of 394 regularly-dialyzed patients in one dialysis center, and incidence of 3.3 percent. This frequency is twice the reported rate of 1.6 percent,and may reflect more accurately the true incidence of this complication.

All 22 patients devleoped symptoms of subdural hematoma after 13 to 14 months of regular dialysis. Six of the present 13 patients had a clear-cut history of head trauma, another six had marked changes in body weight or blood pressure between dialyses, and ten had recent episodes of "blood access" (external plastic arterio-venous shunt, or subcutaneous A-V vascular shunt) clotting or infection, or both. By contrast, the nine previously reported patients had no history of head trauma, no excessive weight shifts between dialyses, and only two had blood access problems.

Based on their own observations, the investigators suggest that the following factors contribute to formation of subdural hematoma: head trauma, ultra-filtration to control excessive accumulation of fluid and hypertension, use of anticoagulants, and frequent vascular access infection and clotting.

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The clinical similarity of subdural hematoma and the dialysis disequilibrium syndrome may produce an initial problem; however, the headache, nausea, vomiting, drowsiness, confusion, and hypertension associated with the latter are either ameliorated or entirely disappear with regular dialysis therapy. Physical findings are unreliable in ascertaining the existence of a subdural hematoma, and, even when they are suggestive, they do not indicate the site of the lesion.

Skull films, lumbar puncture, and electroencephalography were of little diagnostic help. Brain scanning, although valuable and safe, was not as useful as desired due to occurrences of false-negative studies and failure to identify bilateral lesions. Cerebral angiography was always diagnostic. Surgical intervention yielded disappointing results, and only two of 13 patients (15 percent) survived.

NIAMDD grantee Fred L. Shapiro, M.D., of the University of Minnesota Medical School, and his associate Arthur Leonard, M.D., reported their study in the *Annals of Internal Medicine*, May, 1975.

#

Photo Feature

ACCELERATOR PRODUCES ENOUGH PIONS FOR MEDICAL TESTING

Medical scientists are analyzing long-term effects of negative pi mesons (pions) on normal tissues surrounding and underlying nodules in patients who received radiation late last fall at the Clinton P. Anderson Meson Facility, a part of the Los Alamos Scientific Laboratory (LASL) in Los Alamos, New Mexico.

The 800-million-electron-volt accelerator at the Los Alamos Meson Physics Facility (LAMPF) is the only accelerator in the world currently capable of producing pions in sufficient quantities for medical testing. The first tests of pi mesons on cancer patients are being conducted by the University of New Mexico Cancer Research and Treatment Center (CRTC), in cooperation with LASL, under a grant to UNM from the National Cancer Institute, Division of Research, Resources, and Centers. The LAMPF accelerator operations are supported by the Energy Research and Development Administration.

The first radiobiological studies on patients with metastatic nodules in the skin were conducted with four patients from October 22 through December 21, 1974, using low radiation levels to compare the effects of pions with those of conventional X-rays.

According to the principal investigator, Dr. Morton M. Kligerman, CRTC Director, normal skin reactions to X-rays were observed as more intense than reactions to pions. This could be due, however, to differences in uniformity of dose in the treatment area or to the size of the area

(more)

where the maximum reaction occurred. No untoward effects in the normal skin or subcutaneous tissues have been observed.

Scientists are studying pions because of their theoretical advantages in cancer therapy over conventional radiation, such as high-energy X-rays produced by linear accelerators or gamma rays produced by cobalt machines. Unlike X-rays or gamma rays, pions are particles which can be stopped at a predetermined point. Pions deposit relatively small amounts of energy as they travel through the body tissue. This portion of their path is called the "plateau region." As each pion slows, it is pulled into the nucleus of an atom. This makes the nucleus unstable and it explodes, releasing large subnuclear fragments that deposit large amounts of energy. This process is referred to as the creation of a "pion star" and the stopping region is called the "peak region." By adjusting the "peak region" to that of a tumor area, scientists hope to seriously damage tumors while sparing normal surrounding tissues in the plateau region from high doses of radiation.

Investigators at the UNM CRTC have advised against applying results of the initial tests to other types of body tissue. According to Dr. Kligerman, each type of body and tumor tissue has a different reaction to radiation and extensive tests must be done to see how pions will affect different kinds of tissue.

The LAMPF accelerator is currently undergoing extensive refitting. The current for the initial run was deliberately kept low so that induced radioactivity in the accelerator tunnel would not inhibit correction of

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problems identified during the initial test run. The accelerator will be reactivated this fall, and production of much higher dose levels is planned within a short time after reactivation.

Additional skin nodule tests will be conducted with other patients this winter. Studies will then be extended to metastatic nodules in the cervical lymph nodes and the lungs and to large head and neck lesions. Phase I studies will then begin on lesions of the brain (gliomas), pharynx, larynx, oral cavity, esophagus, lung (superior sulcus), pancreas, stomach, bladder, prostate, uterine cervix, rectum, and extremities (osteogenic sarcoma). The research program is expected to continue over several years.

Biology and physics studies are also being conducted at LAMPF, under a separate grant from the NCI to the CRTC. Studies on the effects of pions on cell cultures and on normal and tumor tissues in animals are being carried out to lay the groundwork for clinical trials.

Other biomedical studies are being done at LAMPF under the auspices of the LAMPF User's Group, with membership open to any qualified scientist. The LAMPF User's Group includes 1,000 members representing about 225 university, hospital/medical center, industrial, and government institutions in the United States and 11 foreign countries.

(more)

ACCELERATOR (Cont'd)

David Lake, CRTC Physics Technologist, and Frances Dobrowolski, biomedical physicist, check dosimetry prior to irradiation of patients with pions at the Clinton P. Anderson Meson Physics Facility in Los Alamos. Preliminary human radio-biological studies were conducted with four patients last fall to compare the effects of pions with those of conventional x-rays. (NIH Photo #1477)

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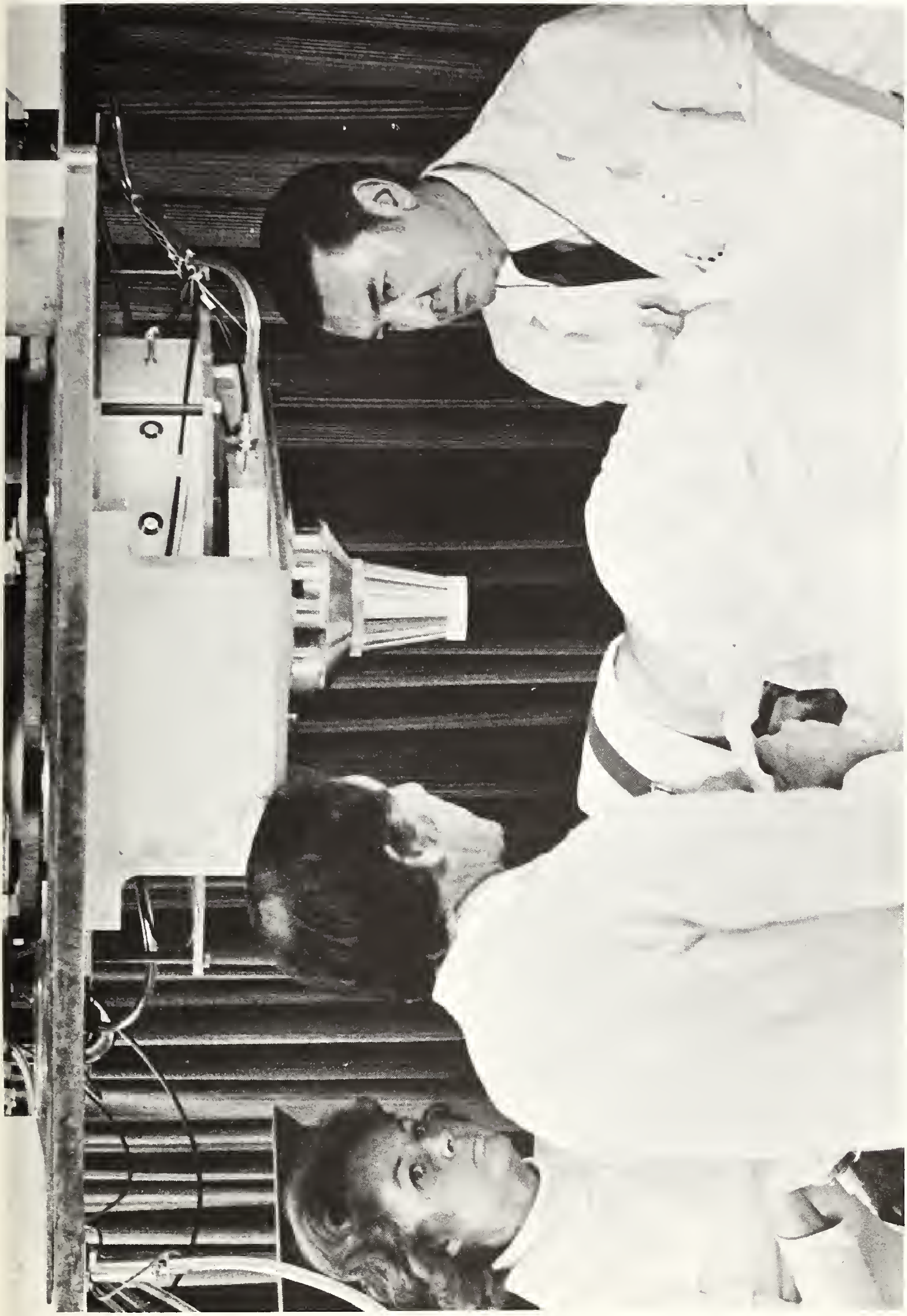

Mrs. Kitty Jones, R.N., CRTC Director Dr. Morton M. Kligerman (left), and Dr. Kenneth Loeffler of Massillon, Ohio, ready a patient for pion treatment at Los Alamos. Tests are scheduled to resume this winter beginning with metastatic skin nodules and progressing to other areas of the body. (NIH Photo #1478)

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News Feature

SCIENTIST TESTS NEW METHOD OF DETECTING GENETIC DEFECTS

A Stanford University School of Medicine scientist is investigating a new method of detecting genetic defects before birth.

Some fetal white blood cells cross the placental barrier into the mother's blood throughout pregnancy. Leonard Herzenberg, Ph.D., professor of genetics, is working out a technique to identify and separate these cells from the mother's cells so they can be tested for inherited defects.

Using maternal blood would be safer than the present technique of amniocentesis which involves sampling fluid directly from the uterus, and entails some risk to the fetus. It could be used for routine screening of pregnant women.

The group will use a highly sensitive instrument Dr. Herzenberg's laboratory helped develop--the fluorescence-activated cell sorter (FACS)--which can isolate cells according to their surface composition.

All cells in the body are covered with antigens, chemical fingerprints unique to each individual. Fetal cells are also coated with antigens, half of them inherited from each parent. Fluorescent antibodies which adhere only to the antigens inherited from the father will distinguish fetal blood cells from those of the mother.

The FACS rapidly separates the labeled fetal cells from the mother's cells and sorts them in test tubes. These cells can be stimulated to grow in the laboratory and can be tested for chromosome defects, or other indications of genetic disorders. The work is supported in part by the National Institute of General Medical Sciences.

#

Photo Feature

VAPOR FROM PRICE LABEL ADHESIVE MAY CAUSE MEATWRAPPERS' ASTHMA

Prepared by Ms. Jeannette Belliveau

Irritating fumes from heat-activated price label adhesive may be the main cause of meatwrappers' asthma, according to Emil Bardana, M.D., at the University of Oregon Health Science Center, Portland.

Medical scientists previously suspected that fumes from polyvinyl chloride soft wrap film cut on a hot wire was the principal cause of reactive airway disease, burning eyes, sore throat, and other irritating symptoms experienced by meatwrappers.

Dr. Bardana and his associates, Drs. Ruediger H. Andrasch, Frederick Koster, and W. Harold Lawson, are the first to suggest that a vapor emitted from thermally-activated price label adhesive causes this type of asthma. Their study was conducted at the University's General Clinical Research Center, supported by the National Institutes of Health's Division of Research Resources. The findings were announced at a recent meeting of the American Academy of Allergy.

The scientists tested the normal breathing capacity of fourteen symptomatic meatwrappers, and then checked their respiratory function under simulated work conditions.

"We set up a meatwrapping machine in a General Clinical Research Center room that simulated almost exactly a typical meatwrapping area," said Dr. Bardana. "It had the same square footage, and like most wrapping areas was not well ventilated. However, facial tissue boxes were wrapped instead of meat."

The tests showed that meatwrappers exposed to polyvinyl chloride fumes

(more)

for three hours had minimal increases in airway obstruction and mild reduction in oxygen saturation in arterial blood. When meatwrappers were exposed to label fumes for as little as five to 15 minutes, however, moderate to marked increases were noted in airway obstruction. Oxygen saturation in the blood also fell dramatically.

The meatwrappers under scrutiny displayed wheezing, shortness of breath, tearing and burning eyes, palpitation, irritability, and upset stomach.

"The fumes from the polyvinyl chloride wrap have some effect, but the heated labels appeared to be the greater of the two culprits," Dr. Bardana said. "We have a feeling that vulnerable individuals may develop a hypersensitivity to a heat-activated substance, but we can't yet prove it."

The researchers found that the hot wire, which does the cutting of the plastic wrap, eventually gets covered with polyvinyl chloride and subsequently emits fumes continuously.

The scientists report that very little information has been obtained from the manufacturers as to the composition of the various heat-activated price label adhesives. "We have fairly reliable information which suggests the presence of elastomers, thermoplastic copolymers, styrene butadiene copolymers, styrene acrylonitrile copolymers, polyphenyl oxides, polysulfones, and phthalic acid plasticizers," they said. "At least one breakdown product of the latter component is a bronchial irritant and may contain a sensitizing allergen."

Bronchial provocation studies were performed after the medical scientists sent a questionnaire to 165 meatwrappers in the metropolitan Portland area.

(more)

ASTHMA (Cont'd)

Many of the 96 workers who responded commented that the label fumes appeared more irritating than the polyvinyl chloride fumes. More than half reported coughing after exposure to fumes, and many reported runny noses, sneezing, nasal congestion, and difficulty in breathing.

The meatwrapping machine set up for the experiments was an older hot wire model, still widely used. Dr. Bardana described alternatives to this model.

"There are cooler wires designed to cut plastic wrap without emitting fumes," he said. "One machine puts the meat in an enclosed unit, and the fumes are sucked out and vented. These machines are available, but are very expensive and require some retraining of meatwrappers."

There are approximately 75,000 meat wrapping employees in the United States, according to union and industry estimates.

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A potential health hazard exists in poorly ventilated areas where meatwrappers are working with polyvinyl chloride soft wrap film and thermally-activated adhesives labels, says medical scientists at the University of Oregon Health Science Center in Portland. Exposure to fumes from labeling machines are more hazardous than fumes from the soft wrap cutting machines. The studies were conducted at the University's General Clinical Research Center which is supported by the NIH Division of Research Resources. (NIH Photo #1479)

(more)

In many old labeling machines, the adhesive labeling process utilizes a heating pad which produces a copolymer action (such as in styrene-butadiene). The vapors from this heating action may induce a reaction in allergy-prone individuals. The investigation into this newly-discovered occupational health syndrome was conducted at the General Clinical Research Center at the University of Oregon. The Center is supported by the NIH Division of Research Resources.(NIH Photo #1480)

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Research Illustrated

A LOOK AT AMNIOCENTESIS, TRAUMA CARE, AND HEART MONITORING

Amniocentesis, the careful drawing of amniotic fluid, is being performed in this photo and on the following page. Cells shed by the fetus can yield important information to scientists, including genetic researchers whose work is funded by the National Institute of General Medical Sciences. (NIH Photos #1481 and #1482)

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RESEARCH ILLUSTRATED (Cont'd)

(See caption on previous page.)

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A biochemical genetics laboratory technician is arranging chromosome karyotypes so that a proper analysis can be made. The National Institute of General Medical Sciences supports genetic research that includes studying some chromosome karyotypes. (NIH Photo #1483)

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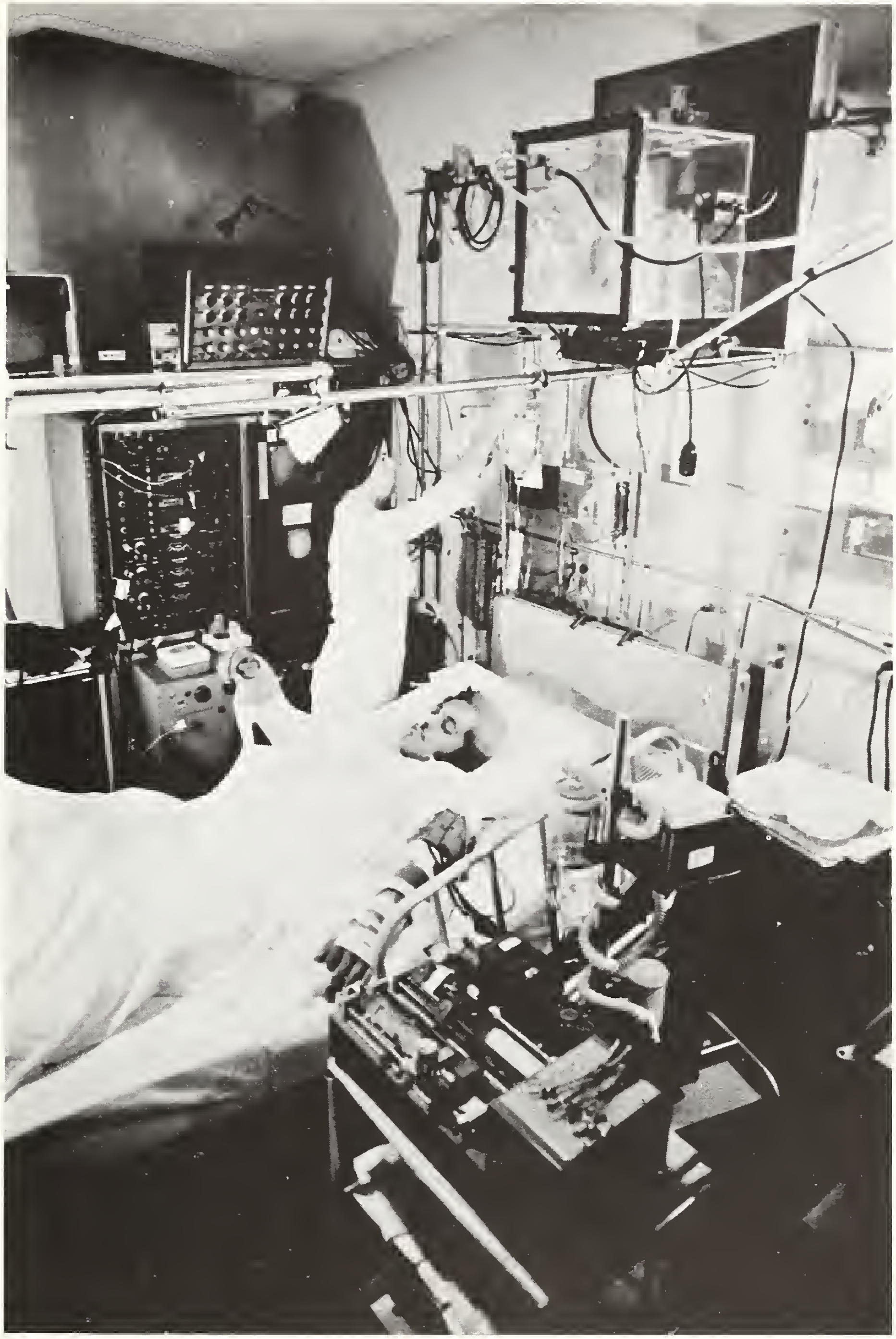

A team of physicians, college engineering professors, and computer scientists is credited with saving the lives of some victims of severe injury who are treated at the Albany Medical Center's Trauma Research Center. The Center receives research support funds from the National Institute of General Medical Sciences. (NIH Photo #1484)

(more)

RESEARCH ILLUSTRATED (Cont'd)

A patient at the Stroke Research Center at the Bowman Gray School of Medicine is shown wearing a tape recorder that takes continuous readings of his heart's activities over a 24-hour period. The recorder, a Holter monitor, makes continuous electrocardiographic recordings of patients who experience transient ischemic attacks (little strokes). Patients can wear the device while doing normal activities at home. Information gained from the recordings will permit researchers to learn more about the relationship between heart disease and transient ischemic attacks. The Center is supported by the National Institute of Neurological and Communicative Disorders and Stroke. (NIH Photo #1485)

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NEWS & FEATURES From NIH

October 25, 1975

Disease Profile

BLACK LUNG DISEASE IS BOTH PROGRESSIVE AND IRREVERSIBLE

Black lung disease or coal workers' pneumoconiosis, is believed to account for more deaths--approximately 1,000 per year in this country--than all other forms of pneumoconiosis combined, and afflicts an estimated 90,000 to 125,000 miners. A recent nationwide survey by the Public Health Service and the Bureau of Mines indicates that nearly 30 percent of working coal miners in the U.S. have black lung disease.

Typically, victims of black lung disease require a decade or more of exposure to mine dusts before they are incapacitated or killed by the disease. In the interim, they experience progressively severe wheezing, coughing, and shortness of breath, and increased susceptibility to colds and other respiratory infections, including tuberculosis, according to the National Heart and Lung Institute.

The progressive, irreversible nature of the disease is revealed by autopsy examination of lung tissues following varying periods of exposure to the mine dusts.

This also shows that the disease actually involves five or more different disease processes:

* Some of the inhaled dusts are retained and become permanently incorporated into the walls of the small air passages (bronchiles) and sacs (alveoli) to form microscopic, focal deposits called *macules*. In aggregate, these macules are grossly visible as blackened patches and streaks in lung slices even following only a few years of dust exposure.

* Destruction of lung tissue around the dust deposits produces a halo

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of emphysema--in effect, a dead air space--around each macule.

* In some patients, scar tissue formation (fibrosis) occurs between macules, and can involve large areas of the lung. While the occurrence and severity of fibrosis are unpredictable, fibrosis has been associated in some studies with exposure to silica dust, and in others with tuberculosis.

* The eventual development of chronic bronchitis and the more generalized forms of emphysema contribute importantly to shortness of breath and disability in coal workers' pneumoconiosis.

* Finally, many afflicated workers exhibit as a complication of their disease elevated blood pressure in the lungs (pulmonary hypertension) and, as a consequence of this increased pressure, compensatory enlargement of the right side of the heart.

Heart failure is the most common cause of death in persons with black lung disease; many others succumb to respiratory failure during an acute respiratory infection.

There is no form of treatment that will halt, much less reverse, the slow course of black lung disease. Available therapy is aimed either at complications of the disease, or at relieving some of its symptoms. Antibiotics are used to treat respiratory infections, and cardiotonic drugs enable the heart to pump more blood through remaining lung tissue. Also available are a number of drugs to ease breathing by dilating air passages or by dissolving obstructive mucus secretions. Research continues on other ways of ameliorating the symptoms and complications of black lung disease.

Prevention is the only known way of controlling black lung disease and, as studies in Great Britain have demonstrated, is quite effective. This is

(more)

accomplished by reducing dust levels in working environments, and limiting the duration of exposure to dust. Specific measure include the use of dust monitoring systems, wetting practices, air filters, dust masks and other equipment to collect or suppress dust at its source or remove it from the atmosphere, improved ventilation systems, rearranging work shifts to reduce individual exposure to particularly dusty environments, periodic X-ray examinations and pulmonary function tests to detect the disease in its early stages, and other screening tests to identify job-applicants and others who are especially susceptible to the disease. People with an hereditary deficiency of the enzyme *alpha-1-antitrypsin* are more likely to develop black lung disease in a particulary severe form in terms of both earlier onset and relatively more rapid progression of the disease. And, for reasons as yet unknown, workers who have either tuberculosis or rheumatoid arthritis together with black lung are especially prone to develop massive pulmonary fibrosis.

Finally, anti-smoking campaigns and above-ground air pollution control activities are (or should be) important elements of any effort to control black lung disease. These additional airborn insults to the lungs aggravate the symptoms and accelerate the course of the disease.

In Great Britain, where coal workers' pneumoconiosis was first described and control measures initiated 30 years ago, mortality and disability from black lung has been halved. Complete control of the disease in this country, including help for those who already have black lung, requires extensive application of known preventive measures and the acquisition of new information concerning the underlying disease processes.

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NEWS & FEATURES From NIH

November 10, 1975

Research Advances

BIOCHEMICAL TEST MAY PREDICT PATIENT'S RESPONSE TO THERAPY

A biochemical test may predict how a patient with acute myelogenous leukemia (AML) will respond to standard chemotherapy, a National Cancer Institute (NCI) physician has reported.

Dr. Bruce A. Chabner, head of the Biochemical Pharmacology Section of the NCI Laboratory of Chemical Pharmacology, discussed the biochemical test at the Seventh International Symposium on Comparative Research on Leukemia and Related Diseases in Copenhagen, Denmark, in October 1975. The meeting is sponsored by the NCI and the Leukemia Society of America, Inc.

The test compares the activities of enzymes in the abnormal white blood cells of AML patients. Enzymes of one type, called kinases, convert two antileukemic agents to their active form. A second type of enzyme, called a deaminase, converts the drugs to an inactive form. AML patients with high levels of activating enzyme and low levels of deactivating enzyme conceivably would have a better response to drug therapy, the NCI scientist suggested.

Acute myelogenous leukemia is a rare form of cancer that occurs primarily in adults and is characterized by the inability of white blood cells in the bone marrow to mature. The result is a marrow packed with abnormal, non-functioning white blood cells called "blasts".

Two anticancer drugs used for inducing remission--partial or complete disappearance of clinical evidence of disease--in AML patients are cytosine arabinoside (ara-C) and 5-azacytidine (5-aza-C). Ara-C and 5-aza-C are similar in chemical structure to the naturally occurring nucleosides, the building blocks of deoxyribonucleic acid (DNA), the cell's hereditary material. The drugs exert their anticancer effect by competing with the

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natural nucleosides for enzymes critical for the synthesis of DNA, thus blocking cell division.

In the study conducted by Dr. Chabner and his coworkers, Drs. Ronald G. Stroller, C. Norman Coleman, Paul Chang, and Kenneth R. Hande, blast cells from previously untreated AML patients were tested for activity of kinase and deaminase enzymes. Three enzymes were measured: deoxycytidine kinase, the enzyme that activates ara-C; uridine-cytidine kinase, the enzyme that may activate 5-aza-C; and cytidine deaminase, the enzyme that converts both drugs to inactive products. Enzyme activities for each patient were expressed as a ratio of activating enzyme to deactivating enzyme.

Forty-four patients with various forms or subclasses of AML took part in the study. The patients had very different potentials for activating and degrading ara-C and 5-aza-C, the NCI scientist found. The enzyme levels varied independently and with no apparent relationship to the subclass of AML or the sex of the patient.

The activity of each enzyme was independent of the activity of the other two. Some patients whose cells failed to activate one drug were able to activate the other drug instead. The study showed that it is necessary to measure activities for both activating and deactivating enzymes in order to determine an individual's potential for response to ara-C or 5-aza-C chemotherapy, Dr. Chabner said.

The biochemical test thus may be useful in selecting which of the two drugs to use for each AML patient. It also may tell whether the patient is likely to respond to either drug. A prospective clinical trial with AML patients is presently underway in cooperation with Drs. Peter Wiernick and Paul Chang at the Baltimore Cancer Research Center to determine whether this test accurately predicts responses to chemotherapy. #

Research Advances

MAYTANSINE SHOWS PROMISE AS AN ANTICANCER DRUG IN ANIMAL TESTS

Maytansine, a compound originally isolated from an East African shrub, shows promise as an anticancer drug in animal tests that precede studies with cancer patients, according to Richard H. Adamson, Ph.D., of the National Cancer Institute (NCI).

Anticancer activity of the Maytenus plant was discovered by scientists in the NCI Drug Research and Development Program: Dr. S. Morris Kupchan of the University of Virginia isolated and identified the compound, maytansine, that was responsible for the activity. Clinical studies of maytansine are scheduled to begin immediately at NCI.

Dr. Adamson, Chief of the NCI Laboratory of Chemical Pharmacology, reported on the toxicology and pharmacology of the naturally-occurring anticancer agent today at the Seventh International Symposium on Comparative Research on Leukemia and Related Diseases, Copenhagen, Denmark, in October 1975. The symposium is sponsored by NCI and the Leukemia Society of America, Inc.

In preclinical tests, the plant product showed activity against a number of experimental types of leukemia cells grown in the laboratory, Dr. Adamson said. These included the human lymphoblastic leukemia line CEM and cells of several mouse leukemias: L1210, L5178Y and P388.

The compound also was active in mice with leukemia P388, mast cell P815 or plasma cell YPC-1 cancers, and in rats with Walker 256 carcinosarcoma.

Maytansine was extremely potent against the animal cancers, the NCI

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scientist said. Doses in the range of 25 micrograms (a millionth of a gram) per kilogram (1000 grams) of body weight were effective in inhibiting tumor growth in rats. This activity on a weight basis was 10 times that of the vinca alkaloids-vincristine and vinblastine-two clinically proven anticancer drugs that may have a mechanism of action similar to that of maytansine.

Studies of the undesirable side effects of the drug suggested that suppression of red and white blood cell formation in the bone marrow may determine the highest doses that cancer patients will be able to tolerate, Dr. Adamson said. Maytansine also caused slight hind limb paralysis and muscular weakness in mice, a clue that suggests the compound may interfere with nerve function. Experiments with pregnant Swiss mice indicated that the compound can cause birth defects.

Experiments at the University of Virginia with dividing sea urchin and clam eggs suggested that maytansine exerts its anticancer effect by inhibiting cell division, Dr. Adamson said. The compound interfered with formation of the mitotic spindles--fine, thread-like projections that form in a cell during division and may be essential for preservation of the cell's hereditary material. Vincristine and vinblastine, originally derived from the periwinkle plant, act in a similar manner. However, maytansine is 100 times more effective than the periwinkle alkaloids in inhibiting cell division, the NCI scientist reported.

When administered to animals, maytansine arrested cell division in a number of organs. It was particularly active in inhibiting dividing

(more)

pancreatic cells. This finding is intriguing, Dr. Adamson said, because no drug now available is very active against pancreatic cancer.

Maytansine is one of a group of chemical compounds called ansa macrolides. Other biologically active ansa macrolides include the antibiotics streptovaricin, an anti-tuberculosis drug, and rifamycin, an inhibitor of a tumor virus enzyme called reverse transcriptase. Maytansine is the only member of this chemical class to show anticancer activity. Physicians hope that the novel chemical structure will endow maytansine with an activity against human cancers that is different from the approximately 50 known anticancer drugs.

#

Research Advances

SPECIFIC RECEPTOR FOR COMPLEMENT IS IDENTIFIED IN HUMAN KIDNEY

A National Institute of Allergy and Infectious Diseases (NIAID) scientific team has identified a specific receptor for C3b -- one of the series of interacting serum proteins known as complement -- in the human kidney's tightly coiled blood vessels known as the glomeruli.

This finding may lead to an understanding of the mechanisms of certain kidney diseases and may assist in the development of appropriate immunotherapy. In glomerulonephritis, for example, the most common type of renal disease, aggregates of antigen, antibody and complement molecules -- immune complexes -- become trapped in the glomeruli. This leads to immune injury due to the subsequent formation of activated cell-destroying complement proteins. The organ's function of purifying the blood is impaired, leading eventually to kidney failure.

Until now, accumulation of immune complexes in the glomeruli was thought to be merely due to their size -- larger than the glomeruli's pores. However, the discovery of this receptor for complement suggests that the complexes containing complement may be specifically bound to the glomerular blood vessels.

The presence of this receptor was discovered because it was observed that only those indicator sheep red blood cells coated with antibody plus C3 adhered to the glomeruli of sections of normal human kidney tissue. Red blood cells coated with the same antibody and other components of complement system did not bind to the kidney tissue. Furthermore, the cells adhered only to the glomeruli and not to other areas of the kidney.

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The investigators also found that only those cells which contained a certain portion of the C3 protein, known as the "b" fragment, would bind to the glomeruli. Additional proof that the receptor is specific for C3b was obtained when binding of C3b coated cells could be almost completely blocked by prior incubation of the kidney tissue with a solution of C3b.

The scientists have not yet found the exact location of the C3b receptor within the glomeruli but it has been suggested that it is located on the surface of the endothelial cell that forms the inside lining of the glomerular blood vessels.

This binding of C3b was observed in all apparently normal kidney tissue examined, including that of a one-day-old child. The presence of this receptor in kidney tissue from patients with various renal disease is currently being studied.

In this study, Dr. Michael Gelfand of Georgetown University Medical Center, a guest worker in NIAID's Laboratory of Immunology, collaborated with two NIAID scientists, Dr. Michael M. Frank of the Laboratory of Clinical Investigation, and Dr. Ira Green of the Laboratory of Immunology. Their findings were reported in the October 1975 issue of the *Journal of Experimental Medicine*.

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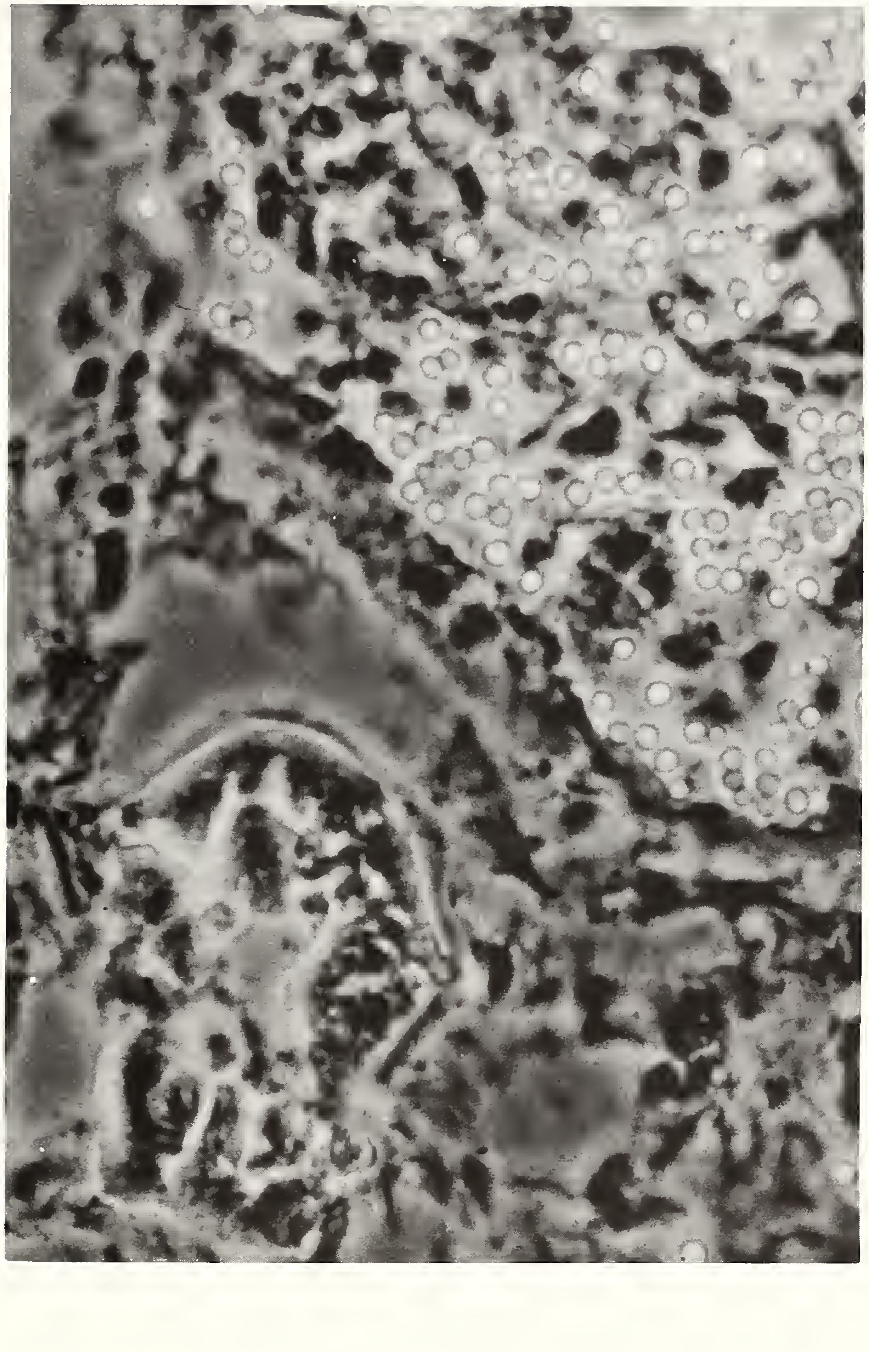

In this section of normal kidney tissue, the ringed sheep red blood cells--which are coated with antibody and complement--are bound only to the clusters of blood vessels in a portion of the glomerulus shown on the right.

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Research Advances

SYSTEMIC ALLERGIC REACTIONS TO FIRE ANT STINGS ARE UNDERRATED

The sting of the imported fire ant, which has invaded more than 150 million acres of 13 southern states, can cause severe allergic reactions, including difficulty in breathing, and periods of unconsciousness. Susceptible individuals can be successfully desensitized to this insect but, in a study partially supported by the National Institute of Allergy and Infectious Diseases(NIAID), a group of allergists in Florida found that the importance and prevalence of these reactions are grossly underrated.

The highly aggressive South American species of fire ants, *Solenopsis richteri* and *Solenopsis invicta,* have become a serious threat to man and animal since their introduction into the U.S. in the early 1900's. These insects attach themselves to the victim by biting him and then pivot about the bite, delivering multiple stings. These stings can be easily identified since the fire ant is the only insect in the U.S. whose sting produces a pustule, a pus-containing eruption.

The Florida allergists reported 49 cases of immediate systemic (whole body) reactions to fire ant stings. The diagnosis of fire ant sting was based on formation of the characteristic pustule and/or skin test using fire ant extract. Systemic reactions were usually indicated by hives and/or angioedema (giant hives). Some patients also experienced difficult breathing, tightness of the chest, wheezing, sweating, nausea, unconsciousness, or itching. These reactions became progressively more severe and life-threatening in six patients.

Thirty-nine patients with severe systemic reactions received desensitizing

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injections of various amounts of fire ant extract. After as little as three months of immunotherapy, ten patients suffered additional bites. Only one individual suffered a systemic reaction, thus indicating a 90 percent success rate.

The Florida group concludes that the threat of systemic reactions can be successfully reduced by proper desensitization shots. However, the availability of this treatment and the severe life-threatening nature of fire ant allergy are apparently being overlooked not only by patients but also by physicians.

Furthermore, the scientists feel that the common practice of equating any ant sensitivity with that of fire ant sensitivity poses a hazard to patients. In this study, one patient suffered a systemic reaction to a fire ant sting while receiving desensitization shots for red ant bites. Until any cross-reactivity (and hence, protection) between the antigens of various types of ants is determined, the allergists strongly recommend testing and treating a patient for specific ant sensitivities.

The researchers hope to provide a more rational approach to the treatment of fire ant allergy by resolving, through laboratory studies, some major problems. These include determining the feasibility of a mixed ant extract, and identifying the antigenic component of the venom which causes the allergic reaction.

The allergists, NIAID grantees Robert B. Rhoades and Heinz J. Wittig of the University of Florida, and the practicing allergists, Walter L. Schafer, William H. Schmid, Paul F. Wubbena, Richard M. Dozier, and Andrew W. Townes, reported their study in the August 1975 issue of the *Journal of Allergy and Clinical Immunology*.

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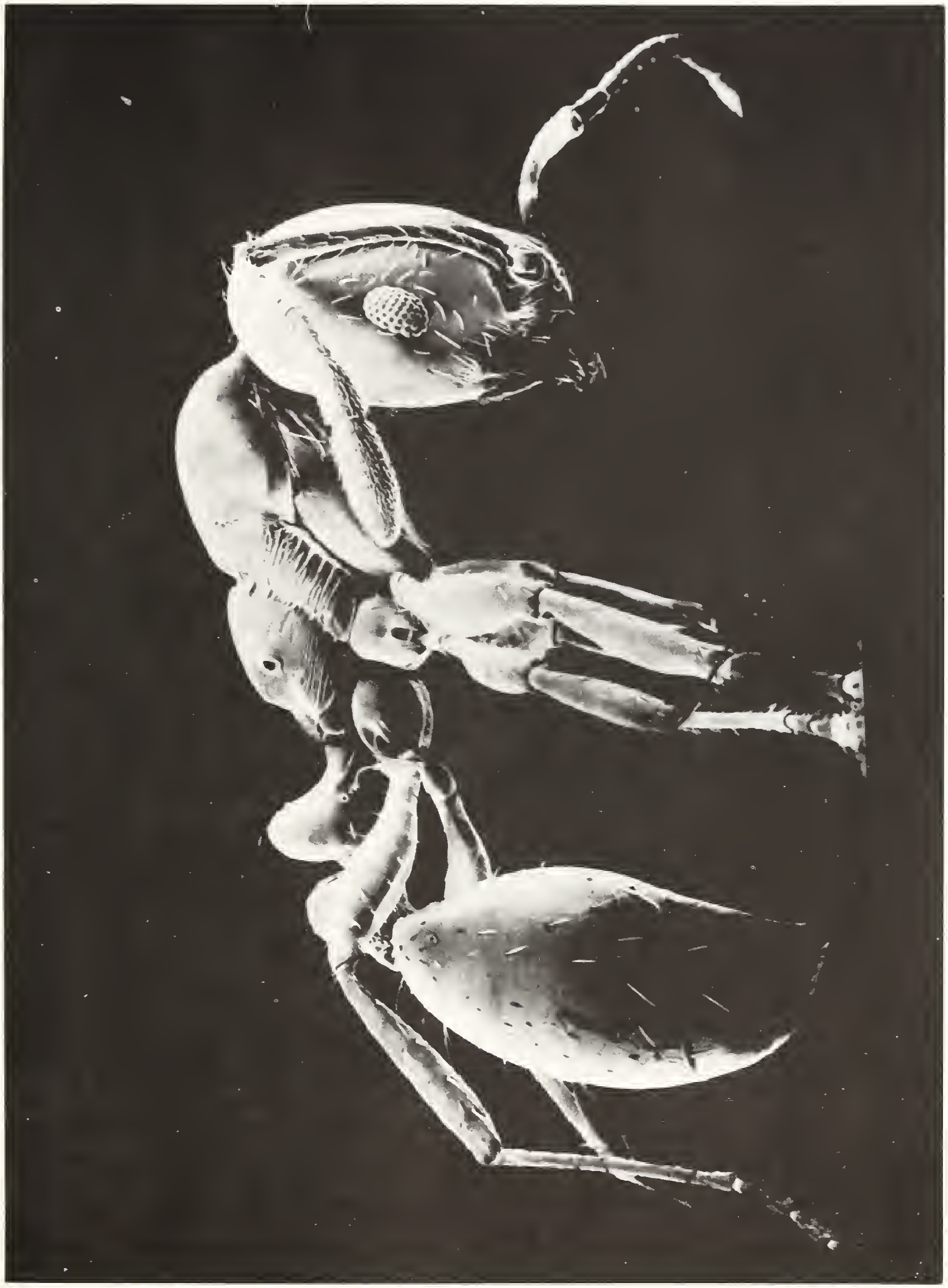

This is a greatly enlarged photograph of a fire ant. (*NIH Photo #1486*)

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GENETIC MATERIAL FOR MOUSE LEUKEMIA VIRUS IS IDENTIFIED

Scientists at the National Institute of Allergy and Infectious Diseases (NIAID) have obtained definitive evidence that a high leukemic strain of mouse contains as part of its normal genetic material the complete genome of the murine leukemia virus. Sisir K. Chattopadhyay, Wallace P. Rowe, Natalie M. Teich, and Douglas R. Lowy of the NIAID Laboratory of Viral Diseases published their work in the *Proceedings of the National Academyy of Sciences.*

Researchers have recognized that certain mouse strains prone to leukemia are chronically infected with viruses that will cause leukemia when injected into other mice. The nature of this chronic infection was examined by NIAID scientists in complex genetic experiments involving two strains of mice -- the high-virus-yielding AKR strain and the non-virus-yielding NIH Swiss strain. Two genes that control the presence or absence of leukemia virus in AKR mice were identified, and the chromosomal location of one gene was mapped.

Molecular hybridization experiments between DNA made from the AKR leukemia virus and DNA from various mouse strains revealed the presence of two classes of virus-related sequences: those present in all strains of mice and those present only in strains that yield virus. The next step was to determine if the genes that control the presence or absence of leukemia virus corresponded to the actual virus-related sequences. The investigators used serial back-crossing to insert the virus-controlling gene into the DNA of virus-negative NIH Swiss mice. Then, using molecular

(more)

hybridization techniques, they verified that these mice also had the virus-specific sequences.

These results indicate that the AKR genes that control the presence or absence of virus are in fact the structural genes for that virus and thus demonstrate definitively for the first time, that at least some oncogenic viruses can be inherited as part of the normal chromosomal genetic material.

This work was also partially supported by the Virus-Cancer Program of the National Cancer Institute.

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November 10, 1975

Photo Feature

COMMUNICATION TECHNIQUE IS DEVISED TO ASSIST RETARDED

They have been called the "hopeless helpless," the severely and profoundly retarded children, often unable to communicate with others or even feed and dress themselves. Joseph K. Carrier, Ph.D., of the University of Kansas Bureau of Child Research, in Lawrence, has developed a highly successful program for these children. He taught almost 200 of them how to communicate without speech using "Non-SLIP," a simplified language with a starting vocabulary of 30 words. Some of the children have even "graduated" from Non-SLIP and can now speak simple sentences.

With Non-SLIP, which stands for Non-Speech Language Initiation Program, Dr. Carrier teaches the child to pick out the correct hardboard symbol from an array on the table, and place it on a response tray. When shown a drawing of a bed, for example, the child must pick out a somewhat bell-shaped symbol. The symbols purposely do not look like the concepts they represent, and the child learns that words themselves are abstract symbols for objects.

When a child makes the right choice, he is rewarded with a hug, a piece of candy, or verbal praise. Wrong selections are ignored. After 19 nouns are learned, the first two verbs are given: "sit" and "stand." Add a few articles and prepositions, and the child is ready to line up the symbols, left to right, to say,"The boy is sitting on the chair."

Most children complete Non-SLIP in about a year. Near the end of the program, many spontaneously begin to purposely make grunts and "aah" sounds, mimicking Dr. Carrier. They are sent to "graduate school," where a speech pathologist helps them to say aloud what they have learned to write with symbols. This research is supported by the National Institute of Child Health and Human Development.

(more)

COMMUNICATION (Cont'd)

Joseph K. Carrier, Ph.D., of the University of Kansas, is shown on this and following pages using his new communication technique that does not require speech. (NIH Photos #1487, 1488, 1489, and 1490)

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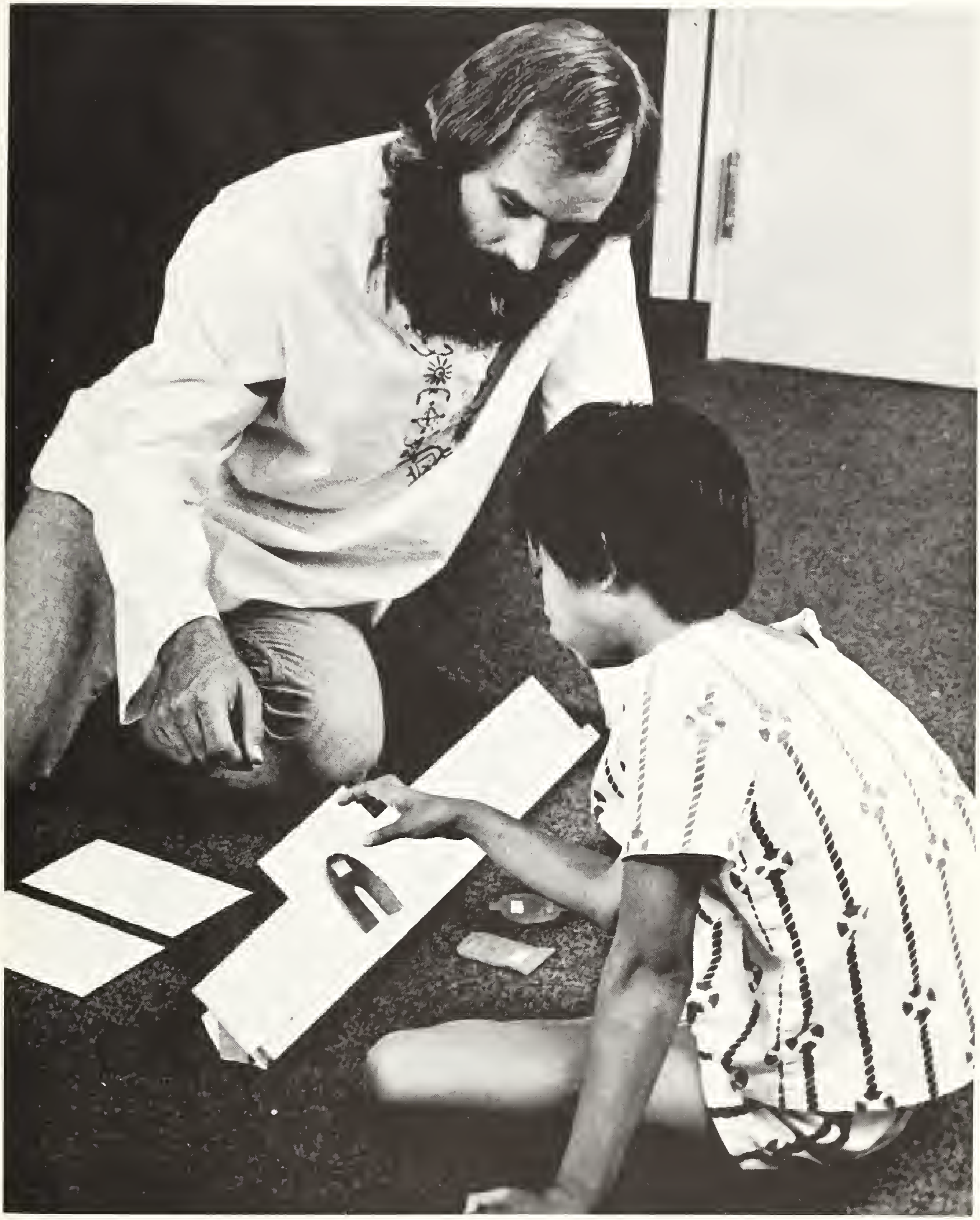

(NIH Photo #1488 - see caption on page 15)

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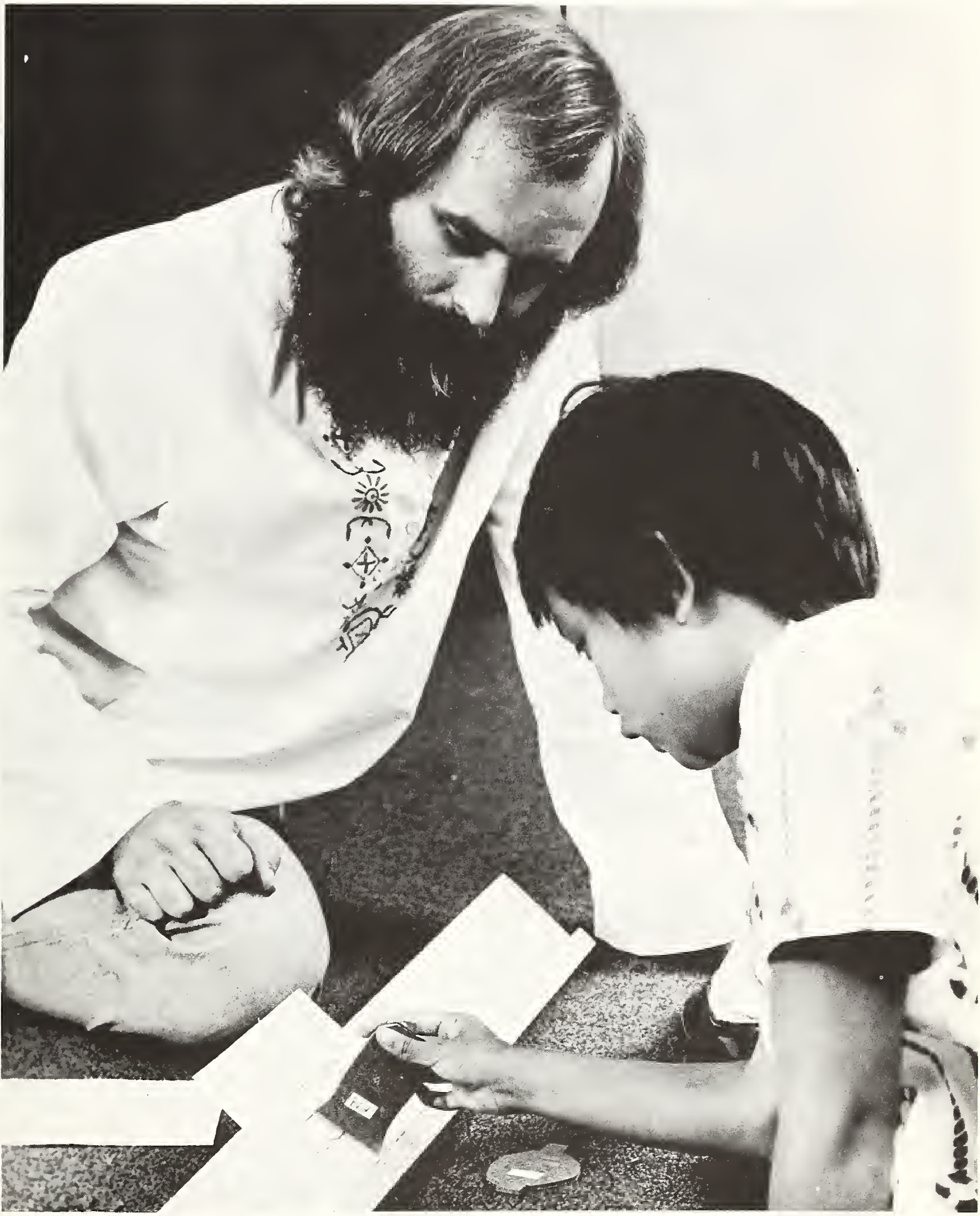

(NIH Photo #1489 - see caption on page 15)

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(NIH Photo #1490 - see caption on page 15)

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News Feature

PREVENTION OF BLINDNESS IS GOAL OF NEW INTERNATIONAL AGENCY

The Fogarty International Center and the National Eye Institute (NEI) will host the first meeting of the Priorities and Projects Committee of the newly-formed International Agency for the Prevention of Blindness (IAPB) at the Stone House on November 12-14.

The IAPB, formed at the request of the World Health Organization (WHO), coordinates and fosters international activities aimed at preventing or treating six eye diseases and problems which account for 80 percent of the world's blindness.

Sir John Wilson of Great Britain, founder and director of IAPB, will keynote the three-day session. Although he is blind, Sir John is an international leader in work for the blind and has traveled extensively throughout the world.

He is founder and director of the United Kingdom's Royal Commonwealth Society for the Blind, and his work in the prevention of blindness includes the traveling medical caravans which last year restored sight to 65,000 cataract patients in India.

The IAPB's Priorities and Projects Committee, chaired by Dr. Carl Kupfer, NEI Director, includes representatives from El Salvador, Ghana, Egypt, West Germany, India, Great Britain, Switzerland, Belgium, and the United States.

At this conclusion of the meeting, the committee will recommend to the Agency's Executive Board specific programs designed to alleviate visual loss caused by the six conditions: trachoma, cataract, glaucoma, onchocerciasis, ocular trauma, and xerophthalmia/keratomalacia.

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In conjunction with this effort, the World Health Organization has designated the theme of next year's World Health Day on April 4, 1976, as "Foresight Prevents Blindness."

The United States Committee of IAPB will also meet on the final day of the international conference. The delegation, which includes six organizations, is chaired by Ms. Virginia Boyce, Executive Director of the National Society for the Prevention of Blindness, Inc. in New York. For further information, contact Ms. Bonnie F. Spellane, National Eye Institute, (301 496-5248).

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NEWS & FEATURES From NIH November 10, 1975

News Feature

FEMALE HORMONES MAY HELP TREAT OSTEOGENIC SARCOMA

Female hormones may be useful in treating osteogenic sarcoma, a rare form of bone cancer striking primarily adolescents.

Drs. James H. McMaster and Pierce E. Scranton, two orthopedic surgeons pursuing this cancer research at the General Clinical Research Center, Children's Hospital of Pittsburgh, contend that hormone treatment opens up a new approach to treatment of this disease. The General Clinical Research Center is supported by NIH's Division of Research Resources (DRR).

"Hormone therapy is significantly prolonging the lives of our terminal patients," says Dr. McMaster. "All seven children who have undergone female hormone treatment at the clinical research center have lived beyond ten months after diagnosis, the point at which most osteogenic sarcoma patients have died. One teenager, for example, continues to lead a normal life almost two years after diagnosis of this disease."

Osteogenic sarcoma is a malignant tumor in the rapidly growing bones of adolescents. Symptoms include abnormal carbohydrate metabolism and above average height. Affecting approximately 1,900 Americans annually--1,100 males and 800 females--this diseases causes death in 85 percent of its victims.

The malignancy seems to stimulate a growth factor, which prompts the production of somatomedin, a liver secretion. Structurally and functionally similar to insulin, an abnormally high level of somatomedin may inhibit insulin activity and cause chemical diabetes mellitus.

Another factor which may cause abnormal carbohydrate metabolism is non-suppressible insulin-like activity. Detected in osteogenic sarcoma patients, its function is little understood.

(more)

HORMONES (Cont'd)

Drs. McMaster and Scranton feel that if excessive growth factors stimulate osteogenic sarcoma, then therapy should strive at suppressing growth factors. The DRR-supported research facility study shows that only 16.6 percent of the male patients live for two years or more, compared with 45.8 percent of the females. Since females seem to have a better survival rate, and female hormones (estrogen and progesterone) suppress bone growth, the doctors decided to try hormone treatment on their terminal patients.

This therapy gradually corrected patients' carbohydrate metabolism defects until their glucose tolerance tests appeared normal. Since the disease seems to stop progressing at this point, correction of carbohydrate metabolism defects in each patient seems to be a characteristic of survival.

Treatment of osteogenic sarcoma also includes surgery to remove the malignant tumor, and drug therapy to prevent the spread of tumors to other parts of the body.

"The three types of treatment are given simultaneously," says Dr. McMaster, "because it is unlikely that any single agent will consistently suppress a given tumor."

After initial treatment at the DRR-supported General Clinical Research Center, the children return home to normal activities. They return to the Clinical Center every three months for evaluation of their therapy.

Since they believe that osteogenic sarcoma could join the list of hormone-responsive cancer tumors, Drs. McMaster and Scranton urge that a national study be undertaken to evaluate the effectiveness of hormone therapy.

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NEWS & FEATURES From NIH November 10, 1975

News Feature

NIEHS INVESTIGATES CERTAIN EFFECTS OF NOISE ON HEALTH

Noise research conducted and supported by the National Institute of Environmental Health Sciences is an integral component of its overall effort to determine what factors in the environment, operating singly or in combination, adversely affect man's health.

General objectives of the NIEHS noise effects program are to increase understanding of physiological, biochemical, and electroneural mechanisms, the disruption of which by noise and other ototoxic agents leads to the cellular and neural damage which characterizes permanent hearing loss; to identify various environmental chemicals, drugs, and other agents which potentiate hearing loss from noise and to characterize the degree and extent of additional loss to be expected; and to investigate specific endocrine, immunologic, physiologic, pharmacologic, teratogenic, cardiovascular, and other mechanisms which may be affected by chronic noise exposure.

Studies have been initiated to explore the location and nature of physiological changes underlying the temporary threshold shift of hearing. The cochlear microphonic, whole nerve action potential and endocochlear potential of noise-exposed guinea pigs were examined to elicit the hearing recovery process. Measuring the electric potential produced by pure test tones following noise exposures at various sound pressure levels showed very evident hearing threshold shifts at the lower test tones and higher noise exposures with subsequent recovery. Prolonged noise exposure would have resulted in a permanent threshold shift in hearing. Evidence gained

(more)

from the temporary threshold shift data will be useful for predicting a permanent hearing loss over an extended pressure time. The next step will be to measure the temporary threshold shift caused by exposure to ototoxic antibiotics, alone and in combination with noise.

Studies also are underway to confirm the ototoxicity of methyl mercury and relate this to the resulting concentrations of methyl mercury found in the cochlear fluids.

A piezoelectric transducer has been developed which, when in direct contact with the ossicular chain, can impart highly defined signals including language into the cochlea. This device avoids the necessity for complex microphonic measurements of sound pressure levels at the tympanic membrane. Concurrently under development are more sensitive methods for measuring displacement of waveform of the ossicular chain and basilar membrane.

Acute noise exposure has been shown to markedly affect various hormone secretions. Immunological function can be affected by altered levels of certain hormones. Studies are being conducted to detect suppression or stimulation of cell-mediated immunity in noise-exposed rodents. Early data shows some suppression of lymphocyte production following noise exposure.

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Research Illustrated

RESEARCH ANIMALS, STUDIES OF LIQUIDS ARE PART OF NIH WORK

A laboratory animal is given a special substance to inhale during research work at the National Institutes of Health. (NIH Photo #1491)

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RESEARCH ILLUSTRATED (Cont'd)

Substances growing in test tubes must be carefully controlled, according to the National Institutes of Health. (NIH Photo #1492)

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Blood typing is shown being performed at the National Institutes of Health. (NIH Photo #1493)

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November 10, 1975

Disease Profile

MOLDS CAUSE SOME ALLERGIC RESPONSES

Prepared by Mary Jo Miller
(A University of Maryland student)

Over 14.6 million Americans suffer with sneezing, itchy, runny noses, and congestion, often called "hay fever". Many people attribute these allergic responses to pollen, but they may also be caused by molds.

Molds, along with yeasts, are types of fungi. While yeasts do not cause allergic reactions, a few dozen of the thousands of different molds trigger the body's immune response mechanism that causes the allergy symptoms.

Researchers in immunology are studying the body's immune response to many things, including foreign tissue, microorganisms, and malignant growths, as well as allergens.

In 1971, the National Institute of Allergy and Infectious Diseases (NIAID) initiated a program of Asthma and Allergic Disease Centers. Seventeen of the Centers have been established to hasten the application of scientific achievements in the immunology field and enable the allergist to provide relief to the allergy sufferer through improved therapy. Studies like these will contribute to better treatment and, perhaps, even cure for all types of allergy, including mold allergy.

Currently, scientists know that a person first becomes allergic to a certain mold by inhaling the "seeds", or reproductive particles of the fungus, called spores. In the nose, the mold spores trigger a reaction in cells in the tissues under the mucous membranes which line the nasal passages. This reaction leads to the symptoms of allergy.

This is because, following one or more exposures to the spores, the cells have become coated with a special type of antibody called immunoglobulin E. While most antibodies help the body fight off foreign invaders, such as bacteria and viruses, IgE antibodies start a harmful reaction in which

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certain chemicals, which are responsible for the allergic reaction, are released. One of these chemicals, histamine, causes the blood vessels in the nose to expand and leak fluids. This results in the familiar runny nose, swelling of the nasal passages, and thus, congestion and difficulty in breathing.

Because they are so small, mold spores may even evade the protective mechanisms of the nose and upper respiratory tract to reach the lungs and bring on an allergic reaction there. Usually, this leads to the buildup of mucus, wheezing, and difficulty in breathing associated with asthma.

Less frequently, inhaling the spores or fragments may lead to other symptoms, such as skin lesions like eczema or chronic hives or a disease known as hypersensitivity pneumonitis, an allergic lung condition which can lead to serious heart and lung problems if the source of the organism involved, Actinomycetes, is not removed. The Actinomycetes are complex forms of bacteria that are very similar to fungi. In all except the very warmest areas of the United States, molds are mostly seasonal allergens, occurring from spring to late fall. However, unlike pollens, molds do not virtually disappear with the first killing frost. Actually, frost encourages certain molds by increasing the amount of dying vegetation on which molds and other fungi grow.

Different molds are prevalent in various locations in the United States. Two NIAID grantees are presently studying the molds in their regions to determine the molds' importance in contributing to allergies. NIAID-supported studies at the University of Michigan showed recently that various air samples contain different molds during different seasons. *Aspergillus*, one of the

(more)

few fungi that may cause several different forms of human illness, including both infections and allergies, was found along with *Penicillium* to be the most prevalent molds found in 150 homes during the winter.

If a person suspects he may have an allergy, the first thing he should do is consult his family doctor to see if the help of an allergy specialist should be sought. The doctor or allergist will first take a complete medical history and check the person's general health. This history will include questions about other allergies, allergies in the family, variations in the allergy symptoms according to weather, time of day, and season of year, and any medication that is presently being taken.

If the allergist suspects a mold allergy is causing the symptoms, he will often conduct skin tests, based on information obtained from the medical history and on his knowledge of which molds, pollens, and other airborne allergens are important in the geographical area.

In the skin test called the scratch test, a diluted amount of the suspected allergen is placed on a small scratch on the patient's arm or back. If the results of the scratch test need clarification, or if no positive results occur, a more sensitive test, the intracutaneous test, may be tried. In this test, a solution of the allergen is injected under the skin.

With either test, a positive reaction consists of a raised red welt, known as a wheal and flare reaction. This should develop within 15 to 20 minutes if that particular allergen is the cause of the symptoms.

If a mold allergen has been identified, or if the allergist still suspects a mold despite negative test results, he may have the patient place mold culture plates around his home and office. If the mold allergen is known, these plates will help the doctor and the patient determine where some of his exposure to molds takes place. If the allergen is not known, the cultures

(more)

may indicate some less common molds for which the physician might test.

For someone allergic to molds, avoidance of the allergen is difficult, but some steps may be taken to reduce exposure. For example, the mold allergy sufferer should avoid "hot spots" around the home, place of business, or recreational areas that are the molds' favorite places to grow. These include areas of deep shade or heavy vegetation, basement, refrigerator drip trays, garbage pails, air conditioning systems, bathrooms, humidifiers, piles of leaves or wood logs, barns or silos, breweries, dairies, any place where fresh food is stored, and old foam rubber pillows and mattresses.

To supplement avoidance measures, the allergist may prescribe medications which will significantly reduce or relieve the irritating symptoms of the allergic reaction. Antihistamines, corticosteroids, and cromolyn sodium are among the drugs he will consider, depending on the nature and severity of the reaction.

If avoidance measures and medications do not control the symptoms of an allergy to mold, the allergist may suggest immunotherapy. Immunotherapy consists of injections of a diluted amount of the allergen, similar to that used in skin tests. A small amount of a very weak extract is injected once or twice a week at first. The strength of the extract is gradually increased, and the injections are given less often as relief from the allergy symptoms is obtained. It usually takes two or three years before significant relief is realized. The injections are then continued until the person has experienced complete relief of symptoms for two or three years. However, some people may have to continue injections for longer periods.

Though all these treatments relieve the symptoms of mold allergy, they do not cure the allergy. Cure and prevention await new developments in immunological research.

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Research Advances

NINCDS SYNTHESIZES COMPOUND THAT CAN DETECT NIEMANN-PICK DISEASE

Scientists at the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) have succeeded in synthesizing a compound which can be used for the rapid detection of carriers and patients with Niemann-Pick disease.

This hereditary disorder is one of a family of nine metabolic diseases in which a specific enzyme defect produces an accumulation of fatty substances called lipids in various parts of the body. In Niemann-Pick disease a deficiency of the enzyme sphingomyelinase causes an accumulation of a lipid called sphingomyelin in the liver and brain, resulting in early death.

The compound proposed by Dr. Roscoe O. Brady, chief of the NINCDS Developmental and Metabolic Neurology branch, and recently synthesized by his associate, Dr. Andrew E. Gal, provides a sensitive and convenient test for detecting the specific enzymatic defect in Niemann-Pick disease. Until now detection of patients with this disease could be accomplished only with costly radioactively-labeled compounds in laboratories equipped with radioactive-counting facilities.

The investigators have also shown that the new compound, which is an analogue of the accumulating sphingomyelin, is useful for prenatal diagnosis of Niemann-Pick disease. It has also been used successfully to identify an unaffected carrier of the defective gene in utero. They reported their findings in the September 25, 1975 issue of the *New England Journal of Medicine*.

(more)

Since the middle 1960's Dr. Brady and his colleagues have made many important discoveries concerning the chemical nature of these lipid storage diseases. Their findings have led not only to diagnostic tests for these diseases but also to an experimental enzyme replacement therapy which has shown promise in early tests on patients with two of these disorders.

Also associated with Dr. Brady in this study were Sue R. Hibbert, and Peter G. Pentchev, Ph.D.

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NIEMANN-PICK (Cont'd)

Dr. Roscoe O. Brady is chief of the Developmental and Metabolic Neurology Branch of the National Institute of Neurological and Communicative Disorders and Stroke. (NIH Photo #1494)

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ROUGHNESS OF COMPOSITE RESTORATIONS HOLDS PLAQUE

National Institute of Dental Research grantees have reported that, in the absence of tooth brushing, plaque covered the surfaces of composite restorations within 24 hours no matter how they had been polished. However, under identical conditions it took more than 72 hours for polished metal fillings and clean, sound enamel in adjacent teeth to acquire comparable amounts of plaque.

The dentists placed composite fillings of acrylic plastic filled with quartz particles in cavities on the cheek side of second premolars, and finished them in one of several ways. They instructed the patients to refrain from oral hygiene for three days and to return at intervals for examination. Then the teeth were repolished by another method and restudied. Thus, the scientists compared the effectiveness of each method under the same clinical conditions in nearly all of the patients.

The teeth were photographed on colored slides before and after tests so plaque-covered areas could be measured with planimeters. Roughness was recorded with a profilometer. Separate specimens, prepared with each technique, were compared in scanning electron micrographs.

Flour of pumice, aluminum oxide, zirconium silicate, and tapered white porcelain stones were used separately with specific finishing cups, points, and felts to smooth the composite surfaces. These were compared with the smoothness of samples of the composite prepared by forcing it to harden under pressure against a strip of Mylar plastic.

(more)

PLAQUE (Cont'd)

The investigators found that composite surfaces were smoothest when the material hardened against Mylar, and roughest when polished with flour or pumice. Of the polishing materials tested, aluminum oxide gave the best results because its particles are smallest, and its hardness is greater than that of quartz.

The scientists consider that composite restorations will continue to collect too much plaque until materials can be developed which take a smoother finish.

These findings were published in the *Journal of the American Dental Association*, July 1975, by R. Terrell Weitman, D.D.S., and Wilmer B. Eames, D.D.S., of Emory University, Atlanta.

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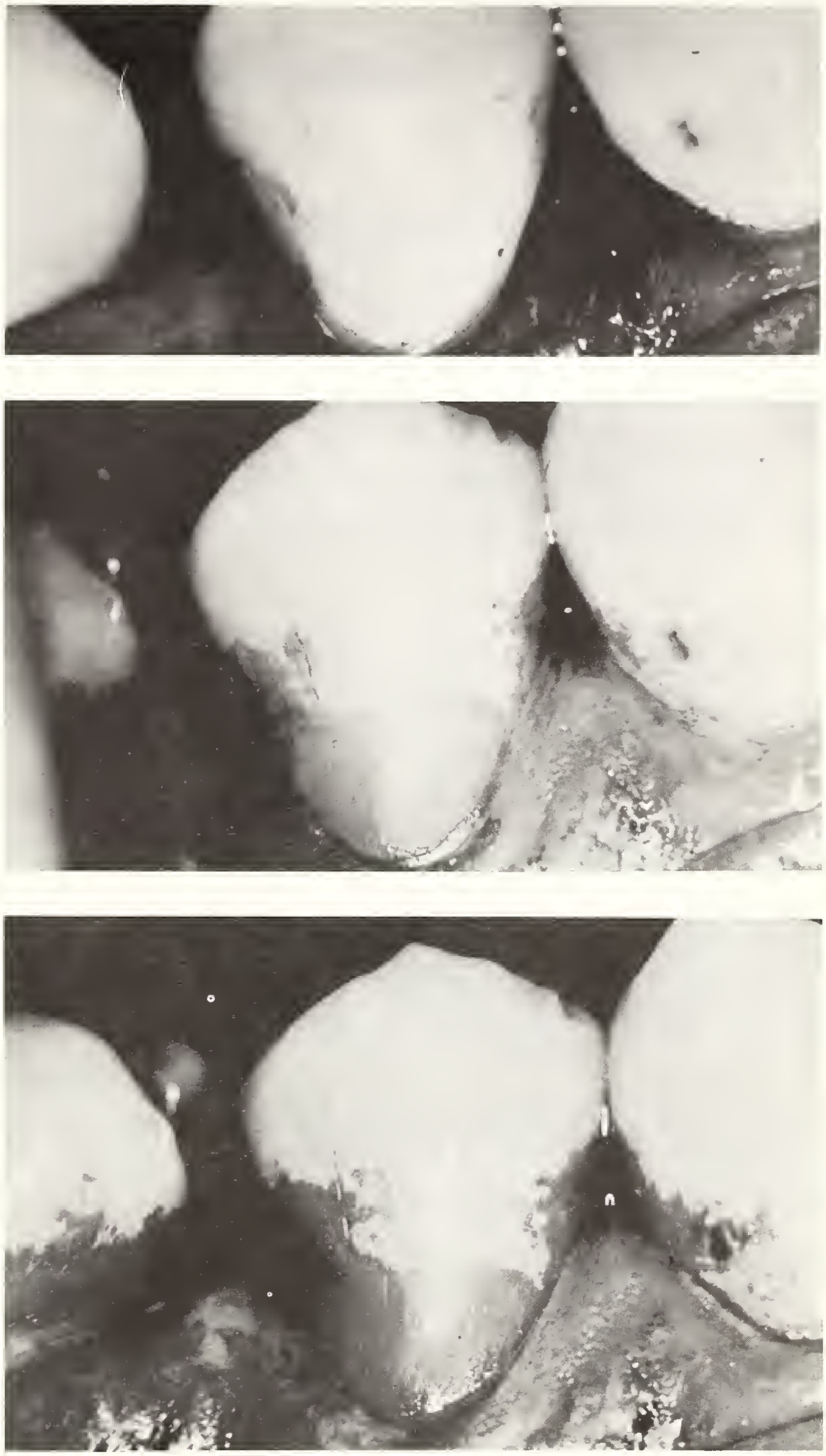

Representative Class V Composite polished with aluminum oxide shows plaque accumulation immediately after insertion (top), at 24 hours (center), and 72 hours (bottom). (NIH Photo #1495)

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Research Advances

NEUROMUSCULAR PROBLEM FOLLOWS CHRONIC USE OF AN ANTIHISTAMINE

National Institute of Dental Research investigators have reported an unusual oral-facial neuromuscular disorder associated with chronic consumption of an antihistamine combined with a decongestant. Two women, aged 55 and 65, took similar drugs regularly for five to 10 years to control nasal discharge. Both developed difficulty in speaking and swallowing, along with uncontrollable head and facial movements, such as bobbing, winking, and mouth gaping.

There was no mental impairment. Both patients improved when they stopped taking the drugs, and grew worse when tested with a similar antihistamine alone.

Metabolic tests indicated chemical derangement of dopamine utilization pathways in a way similar to that found in patients who have involuntary movements induced by phenothiazines. Phenothiazines are structurally and pharmacologically similar to the antihistamines (brompheniramine and chlorpheniramine) which these women used.

The physicians state that antihistamines used occasionally seldom have serious side effects. They are not recommended for prolonged therapy. Apparently some people can develop this delayed type of spastic movement (tardive dyskinesia) if they take these substances daily for years.

Bradley T. Thach, M.D., now at Boston Hospital for Women, James F. Bosma, M.D., of the National Institute of Dental Research, and Thomas N. Chase, M.D., of the National Institute of Neurological and Communicative Disorders and Stroke, reported their findings in the *New England Journal of Medicine*, September 4, 1975.

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Research Advances

SOMATOSTATIN MAY HAVE NO EFFECT ON PLATELET FUNCTION

A California grantee of the National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD) has shown that somatostatin has no effect on either platelet function or the coagulation mechanism in humans. This is in contrast to a previous report that this hypothalamic hormone may have caused hemorrhagic diathesis associated with platelet malfunction in baboons.

Recent research has revealed that the hypothalamic hormone somatostatin decreases both plasma glucagon and glucose levels in diabetic patients and, thus, may prove to be a useful adjunct to insulin. Preliminary studies, however, of the effects of somatostatin in baboons have suggested that this hormone significantly reduces the number of blood platelets and increases the likelihood of bleeding.

Therefore, studies have been undertaken to assess the possible effects of somatostatin on human coagulation and platelet function, inasmuch as the experimental use of this hormone in man is increasing in this country and elsewhere. These studies indicate that somatostatin does not affect coagulation and platelet function in man and that its prolonged administration lacks ostensible toxicity.

Blood samples were obtained for analysis before, during, and after infusion of synthetic linear somatostatin (500 micrograms/hr) for four hours in four patients with juvenile diabetes and in one normal subject. In another experiment, synthetic cyclic somatostatin (500 micrograms/hr) was

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infused for 18 hours in three patients with juvenile diabetes, and blood samples were obtained for analysis in a similar fashion.

Plasma glucose and glucagon levels declined in all subjects during somatostatin infusion, indicating that the preparation used was biologically active. The four-hour infusion had no noteworthy effect on platelet count, leukocyte count, hematocrit, platelet adhesiveness and aggregation, bleeding time, partial thromboplastin time, prothrombin time, and fibrinogen levels. The 18-hour infusion likewise was without adverse effect.

These results, which are at variance with preliminary studies in baboons, may be attributed to a dose-dependent phenomenon (some five to 10 times more somatostatin was used in baboons) or to a species difference. They are supported, however, by the fact that some 200 human subjects have received somatostatin to date without serious toxic effects, including absence of effects on coagulation and platelet function in more than 70 subjects treated by the present investigators. NIAMDD grantee Dr. Peter H. Forsham of the University of California, San Francisco, and associates reported their study in the *New England Journal of Medicine,* Vol. 293, September 4, 1975.

#

Research Advances

ROLE OF ELDERLY IN THEIR RELOCATION IS STUDIED

Do elderly people adjust to relocation more successfully when they have a say in the decision that moves them?

That question was posed in a paper delivered Monday, October 27 at the 28th annual meeting of the Gerontological Society in Louisville, Ky.

The paper, presented by Marion L. Beaver of Los Angeles, represents preliminary findings as part of ongoing research for her doctoral dissertation at the University of Southern California.

Ms. Beaver, one of more than 50 representatives to the conference from USC's Ethel Percy Andrus Gerontology Center, is working toward a Ph.D. in social work. Her research is funded by a grant from the National Institute of Child Health and Human Development.

"The Decision-Making Process and its Relationship to Relocation Adjustment in Old People" further probes theories that older persons who suffer illness after they enter residential care facilities do so because they had relatively little say in the move itself.

Ms. Beaver reported that she is interviewing more than 100 residents of an apartment complex, designed specifically for older persons, where the residents felt they had made their own decision to live there.

She said she studied the differences between those who were adapting easily to relocation and those who were not. Interestingly, she reported, those who found readjustment easier were involved in more activities than were members of the other group.

(more)

ELDERLY (Cont'd)

She said, "Relocation outcomes are more likely to be negative when old people are deprived of an opportunity to participate in the decision making process. While the stress of moving for an old person should not be underestimated, neither should their resilience and ability to participate in decisions about their lives."

The paper was part of a session on Social Research, Planning and Practice, Community Living, and Physical Environment.

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Research Advances

EFFECTS IN AGED OF SOME HYPERTENSION DRUGS NOTED

Kathleen C. Light, a doctoral candidate in psychology at Syracuse University, has called for further study into the effects of medication prescribed for high blood pressure. While many medications are successful in reducing the risk of eventual stroke in patients with hypertension, all their side effects are not known.

Her words of caution were part of a paper prepared for delivery at the 28th annual meeting of the Gerontological Society at Galt House on October 28, 1975, and were based on research which comprised her master's thesis. Ms. Light, a research assistant at the All-University Gerontology Center at SU, was at first interested in finding out if persons with high blood pressure (hypertension) showed evidence of brain cell damage by reacting more slowly on timed tests than those with normal blood pressure. Brain damage can occur, she said, anytime there is an interruption in blood flow to the brain.

Ms. Light divided the hypertensive subjects she tested into two groups: those who had been taking drugs to control blood pressure and those who had not. She expected to find that those who had been previously medicated would react faster on the timed tests than those who had not been medicated because medication is known to reduce the chance of complications from hypertension and therefore the chance of damage from loss of blood flow to the brain. But she found the reverse was true. Those who had been medicated were slower on the tests.

In addition, older subjects were slower than younger subjects.

(more)

HYPERTENSION DRUGS (Cont'd)

"It's important to note," Ms. Light emphasized, "that not all the hypertensive subjects in any group were slowed. Many subjects with high blood pressure reacted as quickly as the healthy subjects on these tests." She is currently retesting some of the nonmedicated patients from her first study to see how they have changed after starting medication. She is also at work on another project designed to study changes in cerebral blood flow in patients who have suffered strokes.

Ms. Light's research was performed at the State University of New York Upstate Medical Center, Syracuse, N.Y. It was supported by grants from Marion Laboratories of Kansas City, Mo., the Veterans Administration Hospital in Syracuse, and the National Institute on Aging.

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NEWS & FEATURES From NIH

November 25, 1975

Photo Feature

NIH STUDIES FREE-RANGING MONKEYS IN NATURAL HABITATS

The University of Puerto Rico's Caribbean Primate Research Center, supported by the National Institutes of Health Division of Research Resources (DRR), offers scientists an opportunity to study intact groups of free-ranging monkeys in natural island habitats.

Nowhere else can researchers find a stable, wild monkey population of known genealogy plus a "ghost" troope of boxed, labeled skeletons from a complete social group.

Cayo Santiago, oldest of the primate center island colonies, is less than a mile from Puerto Rico's southeast coast. Started in 1938 when 400 rhesus monkeys from India were tatooed and released on the island, research is devoted to observational investigation of the primates. The Caribbean Center's policy forbids experimental manipulation of the Cayo Santiago animals and limits the number of people visiting the island. Handling is restricted to an annual trapping session when yearlings receive identification tatoos and blood samples for genetic and other studies are taken.

Research policy at the La Parguera site, which consists of two other small primate center islands on Puerto Rico's southwest coast, allows surgical and drug intervention, particularly when scientists plan to observe subsequent social interactions.

One of La Parguera's islands houses the breeding colony developed in 1974 under the U.S. Food and Drug Administration's first contract to domestically breed rhesus monkeys. Aimed at offsetting an anticipated shortage of wild-capture primates from Asia and South America, the 1,000 primates should eventually produce 500 young rhesus a year for vaccine testing and other FDA purposes.

(more)

MONKEYS (Cont'd)

Although rhesus monkeys predominate, small groups of capuchins, cynomolgus, and squirrel monkeys are maintained by the DRR-supported research center. The only free-ranging colony of patas monkeys in the Western Hemisphere live on one of the La Parguera islands.

Research by resident and visiting scientists at the Caribbean Center includes the following work:

*Dr. William T. Kerber, Scientific Director, is studying the reproductive physiology of the squirrel monkey colony.

*Using castrated rhesus monkeys, Dr. James Loy of the University of Rhode Island, finds that castrates fight, play, and lack definitive mating seasons. Control group males are vasectomized to keep pregnancy, offspring, and maternal behavior from destroying the validity of the control situation.

*In an investigation of the effects of a marihuana component on social and sexual behavior of semi-free-ranging rhesus monkeys, Dr. John Vandenbergh, a North Carolina scientist, expects to aid in the development of animal models for testing heroin and other drugs of abuse.

*Using the skeleton collection, blood samples drawn during the annual trapping session, and other sociometric and genealogical data, three scientists are confirming the presence of inherited traits among nonhuman primate social groups.

All of the Center's islands provide their primate inhabitants with commercial monkey chow and food supplements. Drinking water is piped from rainwater-collecting tanks.

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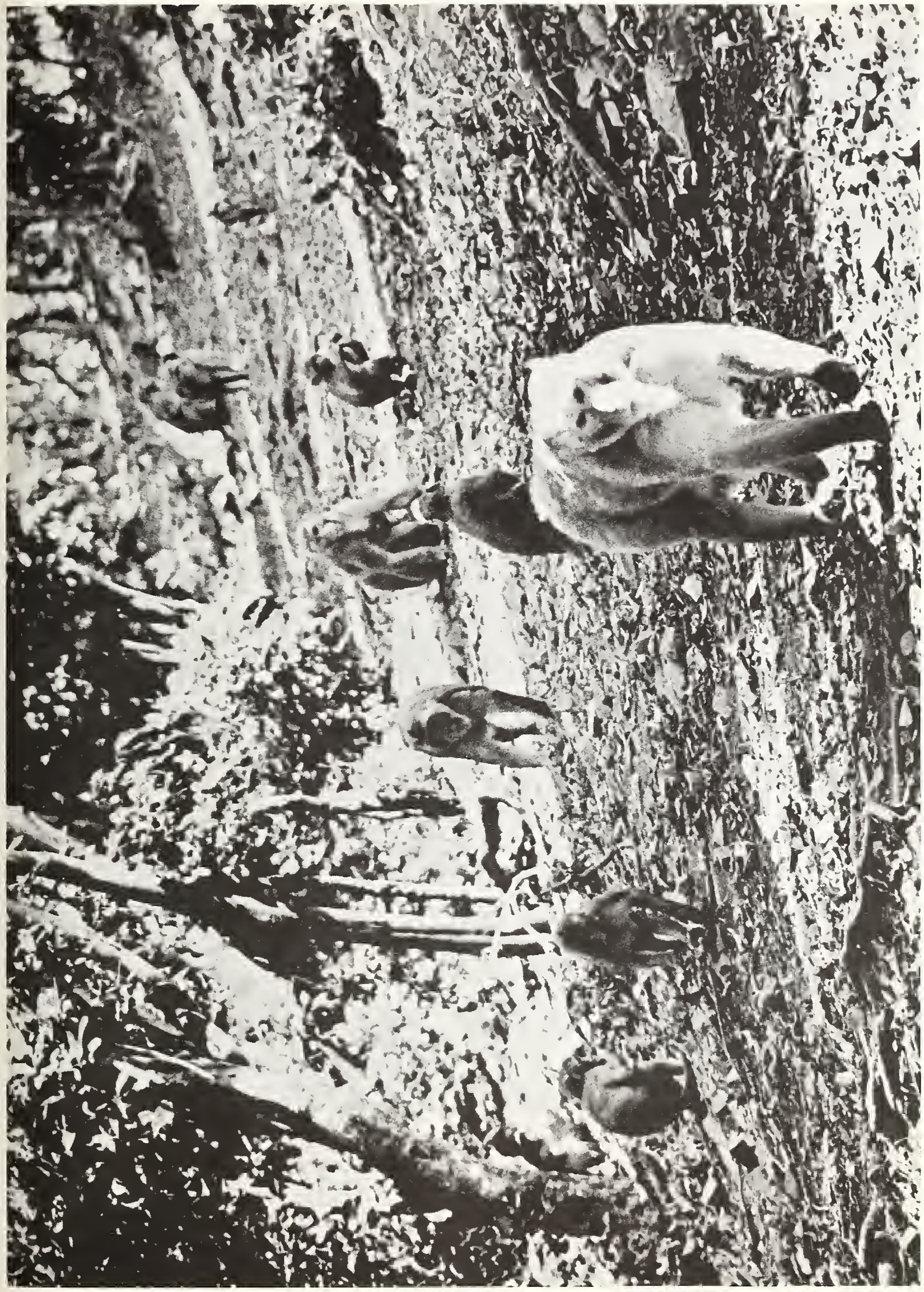
MONKEYS (Cont'd)



The Center's animals have virtually unrestricted access to all portions of their island. Group movements and the displacement of one social group by another are among the activities recorded in daily observations. (*NIH Photo #1496*)

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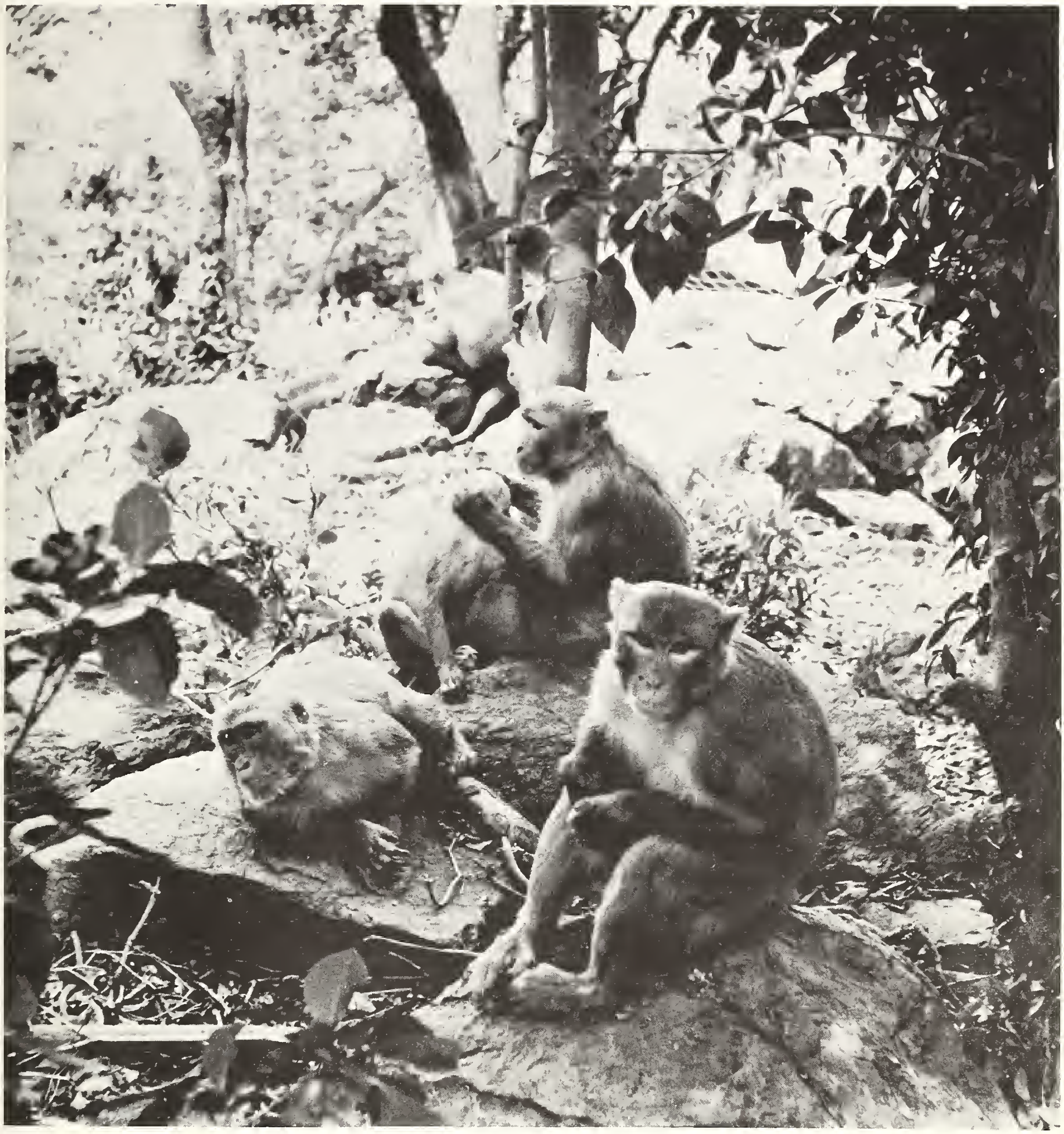
MONKEYS (Cont'd)



An undisturbed existence in a natural habitat is the lot of rhesus monkeys born into the colony at Cayo Santiago. Lifelong identification of each of these research animals is made possible, however, through tatooing in infancy. No monkeys have been added since the initial release 37 years ago, and none removed for the past four years. (NIH Photo #1497)

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News Feature

TOLEDO SCIENTISTS CHECK EXTENT OF HEART DAMAGE

A group of 19 researchers at the Medical College of Ohio, under contract with the National Heart and Lung Institute, are attempting to develop a technique that uses radioactive isotopes to determine how much heart muscle tissue is destroyed in heart attacks.

Such tissue destruction, or "infarction," occurs when the blood supply to a portion of the heart is halted, usually by accumulation of cholesterol and other fatty material inside the coronary arteries.

The damaged tissue becomes soft and mushy like the rotten spot on an apple. It subsequently is replaced by fibrous but nonfunctioning scar tissue.

Precise determination of the size of infarct is growing in importance because of indications that heart attack damage may be at least partially reversible. Nitroglycerin and other drugs recently have been proposed for administration during the acute stages of a heart attack to limit the amount of heart muscle damage.

But to determine whether such drugs are effective doctors must have some technique enabling them to monitor the size of an infarct so that they can observe whether the zone of tissue damage really does decrease as a result of the drug's administration.

Efforts at perfecting such a technique will make up a substantial part of the MCO project, which extends over two years.

Chief investigator will be Richard F. Leighton, M.D., professor of medicine and chief of the section of cardiology. James N. Ross, D.V.M., Ph.D.,

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associate professor of physiology, will be project coordinator and co-investigator.

The MCO project will involve use of two radioactive isotopes, technetium 99 (Tc-99m) and thallium-201 (Th-201). Both materials, when injected into the blood stream, travel to the heart.

Tc-99m concentrates in infarcted areas, giving off radiation that can be recorded visually on a radiation detection device. Th-201 is picked up by all parts of the heart except infarcted areas, so that damaged tissue appears as a "hole" or a void when examined with scanning devices.

By monitoring the radiographic appearance of the two isotopes, the MCO group also will be monitoring the size of infarcts.

Dr. Leighton said that initial work will use laboratory animals to develop and standardize procedures for Tc-99m heart scans. Although Tc-99m has been used extensively in clinical medicine in brain scans to detect tumors and other brain disorders, and lung scans to detect pulmonary embolism, its use in heart disease for revealing infarcted areas is relatively new.

Thus, substantial uncertainty exists over when the earliest satisfactory images of an infarct can be obtained, how accurately Tc-99m heart scans compare with currently available techniques for estimating infarct size, and other matters.

Dr. Leighton pointed out that techniques such as sophisticated electrocardiograph procedures involving 60 or more leads, rather than the usual 12, and enzyme studies in which there is a correlation between amount of a certain enzyme in the blood and extent of heart muscle destruction, can be used to

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estimate infarct size. But all have limitations and drawbacks.

Dr. Ross noted that the MCO project also will involve basic research that will attempt to determine the point of which damage to heart muscle cells becomes irreversible.

Researchers now think that, although some cellular changes caused by a heart attack may become irreversible within a matter of minutes, others might require much longer periods of time. The administration of appropriate drugs during this period thus might restore some areas of an infarct to full-function, he said.

The group also will try to answer others questions about heart muscle physiology.

Dr. Leighton said that the radioisotope technique could also have other clinical uses. It might, for example, be used to determine the size of an infarct in patients who have just suffered a heart attack.

The information could be used to help predict the likelihood of complications, whose frequency increases with increasing heart muscle damage. The technique could also be used to help select candidates for coronary bypass surgery.

Involved in the project will be the MCO departments of medicine, surgery, physiology, pathology, radiology, neurosciences, anatomy, biochemistry, and the animal research facility.

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NEWS & FEATURES From NIH, November 25, 1975

News Feature

"TOXO" PARASITE CAN INFECT MANY AMERICANS

Not all parasitic diseases are rare and tropical. Toxoplasmosis, for example, is a little known but widespread infection that is found throughout the world. An estimated 30 to 50 percent of all adult Americans become infected by the "toxo" parasite at some time during their lives.

Toxoplasmosis is caused by a single cell animal, a protozoa, called *Toxoplasma gondii*. This parasite was first discovered over 60 years ago in a small African rodent, the gondi. Although scientists of the National Institute of Allergy and Infectious Diseases have long been familiar with the disease and the causative parasite, public concern began more recently. This disease can be a special problem during pregnancy.

T. gondii is still one of the least understood parasites of man and domestic animals. Although the disease it causes is quite common and usually not harmful, it can, under certain circumstances be dangerous or even fatal. Toxoplasmosis usually runs a mild course, and the symptoms become less pronounced as the individual's immune system matures. When symptoms do occur, they may resemble infectious mononucleosis or the common cold. Sometimes *T. gondii* can cause retinitis, an inflammation of the retina of the eye.

But toxoplasmosis is most dangerous when a pregnant woman contracts it. Like German measles, toxoplasmosis may severely damage an unborn child even though the disease causes only a mild or symptomless infection in the mother. In infants infected before birth, congenital defects (such as eye and brain damage) are frequent, and death is not uncommon.

These prenatal infections are probably spread initially throughout both the mother and the fetus. As the mother's protective antibodies are produced and shared with the fetus, the parasites are more and more limited in what

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damage they can do to various organs. An exception is the brain which does not receive the same share of maternal antibody protection as does the rest of the fetal body. Thus, the parasites may continue to live and do their damage in the brain longer than elsewhere in the body.

Research on toxoplasmosis transmission has shown that many animals harbor the parasites in their tissues and organs with no harm to themselves. In addition, the organism lives in raw red meat after slaughter until the organism is killed by heat, drying, or prolonged freezing. Eating raw or undercooked meat is believed to be one way that Americans get toxoplasmosis.

Recent studies have implicated common household cats as a source for human infections. The cats eat infected birds or rodents, resulting in multiplication of the parasite within the cat's intestine. (Cats are believed to be unique in providing a suitable environment for such parasite multiplication.) The cats then excrete the parasites in the form of small sac-like capsules (known as oocysts) within the cats' waste material. Then it is possible for humans, such as the person who changes the litter box, to come in contact with the parasites and become infected.

Cats free of infection can probably be maintained infection-free by not feeding the cats raw meat or undercooked table scraps. In addition the cats should not be allowed to hunt mice or come in contact with other cats that might be infected. These strict precautions are probably necessary only in a household where a woman is or plans to become pregnant.

More facts about the role of cats and other animals in the transmission of toxoplasmosis are being sought by scientists. People, especially pregnant women, who suspect that they have toxoplasmosis or any other adverse health condition should not hesitate to consult their physician promptly.

#

Research Illustrated

US-USSR JOINT COMMITTEE FOR HEALTH COOPERATION MEETS AT NIH

The Fourth Session of the US-USSR Joint Committee for Health Cooperation was held October 20 to 24 at the National Institutes of Health.

Medical scientists from the United States and the Soviet Union presented detailed reports of their work in five major areas of research collaboration: heart disease, cancer, environmental health, arthritis, and influenza and acute respiratory disease.

The scientists also presented - for Joint Committee review, amendment, and approval - their work plans for the coming year. Co-chairmen of the Joint Committee were Dr. Theodore Cooper, Assistant Secretary for Health, U.S. Department of Health, Education, and Welfare, and Dr. Dimitri Venediktov, Deputy Minister of Health, USSR Ministry of Health.

The Joint Committee concluded its deliberations with a public ceremony at which the report of the Fourth Session was signed by Co-chairman Cooper and Venediktov.

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The Soviet scientists were led by Dr. Dimitri Venediktov (center), Deputy Minister of Health, USSR Ministry of Health. (NIH Photo #1498)

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The American researchers were led by Dr. Theodore Cooper (center), Assistant Secretary for Health, U.S. Department of Health, Education, and Welfare. (NIH Photo #1499)

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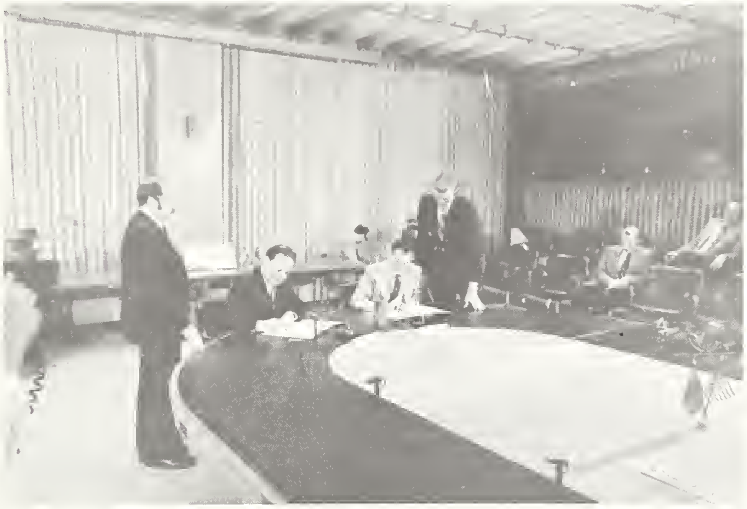

Co-Chairmen Venediktov and Cooper signed the report of the Fourth Session of the US-USSR Joint Committee for Health Cooperation. The signing ceremony took place immediately after the final deliberations. (NIH Photo #1500, 1501, and 1502)

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During the Joint Committee meetings, Soviet and American television crews recorded selected portions for public viewing. Here a Soviet crew is taping a discussion with Co-Chairmen Cooper and Venediktov. The program was aired in Russia the next day at 9 p.m. (NIH Photo #1503)

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Disease Profile

ULCERATIVE COLITIS IS STUBBORN INFLAMMATORY DISEASE OF COLON

Ulcerative colitis is a progressive, inflammatory disease of the colon, or large bowel. Affected persons may suffer from cramps, repeated bloody diarrhea, weight loss, anemia, and potentially fatal loss of body fluids and minerals. A stubborn disorder, difficult to control, that primarily affects young adults, ulcerative colitis also causes unhappiness and misery for thousands of individuals of all ages.

The cause of ulcerative colitis is not known and, as yet, there is no permanent cure. The disease has been attributed to infections, to emotional or psychological disorders, to sensitivity to certain foods or food products, and to a so-called "autoimmune process", in which the body's defense mechanisms attack its own tissue. In recent years, much evidence has accumulated to incriminate autoimmunity, although a primary role for such a mechanism has yet to be demonstrated.

Characteristically, ulcerative colitis attacks individuals during their formative and most productive years, with 75 percent of the cases developing before the age of 40. It frequently affects children, however, and is seen occasionally in aged persons. Females are affected more often than males, and there is some evidence that the disease may run in families.

A diagnosis of ulcerative colitis is usually based on the patient's medical history and an adequate stool examination. The diagnosis then is confirmed by a visual instrumental (sigmoidoscope) examination of the diseased area. Other diagnostic aids include X-rays, blood counts, and determinations of serum levels of electrolytes and other substances. Although a diagnosis of ulcerative colitis is strongly supported by these procedures, it cannot

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be considered firmly established until several other conditions which mimic the disease have been excluded.

Ulcerative colitis varies in severity and is characterized by frequent remissions and recurrences. This characteristic often makes it extremely difficult to evaluate the results of specific treatments. Despite these remissions and recurrences, eight of every 10 patients are usually able to manage their disorder.

Treatment must be on an individual basis, as what may help one patient may not help another. Prime objectives are to correct the constant loss of nutrients, control diarrhea, prevent infection, and minister to the psychologic needs of the patient.

Generally accepted methods of treatment include bed rest, a high protein-low roughage diet, antispasmodic, corticosteroid, and antibiotic drugs, and, in some severe cases, surgical removal of the affected section of the bowel. Drugs which combine antibiotic and anti-inflammatory properties are prescribed.

Few disorders require more medical skill than ulcerative colitis, and only rarely is a complete cure achieved. The goal attained in most patients is control of their symptoms and sufficient rehabilitation to permit reasonably normal living. Long-term medical follow-up of patients with ulcerative colitis (even after remission of the disorder) is very important, since this disease carries with it a higher-than-normal incidence of cancer of the colon or rectum.

The Federal Government's program of research in gastrointestinal disorders such as ulcerative colitis is centered in the National Institute of Arthritis, Metabolism, and Digestive Diseases. Currently, the Institute supports through grant funds several dozen direct and indirect research studies of

(more)

ulcerative colitis at a number of research and medical centers throughout the country.

Research progress in a disease as complex as ulcerative colitis is slow, tedious and far from dramatic. Bit by bit, however, new knowledge is gradually emerging about the disease, as well as improved methods of treatment.

In recent years the potent corticosteroid drugs have become important in the medical management of ulcerative colitis. These agents are usually administered orally, by enema, or by injection. The large, continuous doses required, however, often cause undesirable side effects.

University of Texas scientists receiving Institute support have completed a ten-year study which showed that administration of these drugs in the form of suppositories is more effective than conventional modes of administration in certain patients. Upon periodic reexamination throughout the study period, most patients treated in this manner were found to be in remission or their disease was under control, while only minimal side effects of the drugs were noted. Although this method of treatment was first introduced into medicine by British scientists, the Texas investigators are generally credited with establishing its long-range beneficial effects.

Other Institute-supported studies are devoted to the causes of ulcerative colitis in the hope of learning how to prevent it, some to its precise effect on bodily processes, and others to methods of curing the disease, or at least to making its victims more comfortable.

During the past decade the theory that the disease may have an autoimmune basis has gained more favor. Lending support to this proposal is the knowledge

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that ulcerative colitis may appear in conjunction with a number of different diseases which are associated with hypersensitivity (a condition in which the body reacts abnormally to foreign substances).

One of the foremost advocates of the autoimmune theory is a University of Chicago investigator whose work has long been supported by the Institute. This scientist has observed some improvement in ulcerative colitis patients who were treated with immunosuppressive drugs, agents which suppress the body's natural tendency to fight off attacks by foreign substances. Although it has been difficult to attribute any clinical improvement noted directly to such drugs, these findings are considered presumptive evidence of an autoimmune state.

Evidence obtained to date is, as yet, inadequate to establish a primary causative relationship for autoimmune mechanisms in ulcerative colitis. Knowledgeable researchers believe, however, that recent findings are sufficiently intriguing to warrant continued investigation of the problem.

The fact that ulcerative colitis patients may improve, for one reason or another, would seem to indicate that the disease may be controllable and, perhaps, curable if the cause or causes can be precisely determined. With the present upsurge in organ transplantation it may even be possible in the future to transplant such gastrointestinal organs as the colon in an effort to replace a chronically diseased portion. Much more must be learned about the causes and course of development of ulcerative colitis, however, before the possibilities of more effective control, prevention or cure can be realized.

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Research Advances

EMBRYO TRANSFER TECHNIQUE IS SUCCESSFUL IN BABOON

The first step toward application of embryo transfer techniques to the production of nonhuman primates for biomedical research was made with the successful transfer of an embryo (fertilized egg) from one female baboon to another. The "foster mother" carried the fetus from the fifth day after its conception until the baboon infant was delivered by Caesarean section following the normal gestation period.

This is the first nonhuman primate infant known to be produced by embryo transfer. The transfer was made March 20, 1975, at Southwest Foundation for Research and Education in San Antonio, Texas. The male infant, delivered September 5, 1975, weighing 875 grams (30.6 ounces), appears entirely normal.

The study was supported by the National Institutes of Health Division of Research Resources through its Animal Resources Program. Principal investigator on this project was Duane C. Karemer, DVM, Ph.D., associate professor in the College of Veterinary Medicine, Texas A&M University. Gary T. Moore, DVM, and Martin A. Kramen, Ph.D., were the co-investigators on the project.

The embryo was removed from the donor animal, using a surgical flushing technique, and the transfer was made to the recipient uterus following surgical exposure of the uterus.

Dr. Kraemer was the first to apply embryo transfer techniques to the commercial production of purebred cattle in August, 1971. He reports that procedures used in the baboon are very similar to those which are being

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applied by various companies around the world for increasing the number of offspring from outstanding cattle.

The significance of this research is its potential for helping to improve human health by increasing the productivity of the individual nonhuman primates which possess special genetic characteristics that make them particularly valuable as models for the study of human disease.

One example of possible future application of this embryo transfer technique is to produce specific strains of nonhuman primates for biomedical research on such human diseases as atherosclerosis, diabetes, and cancer.

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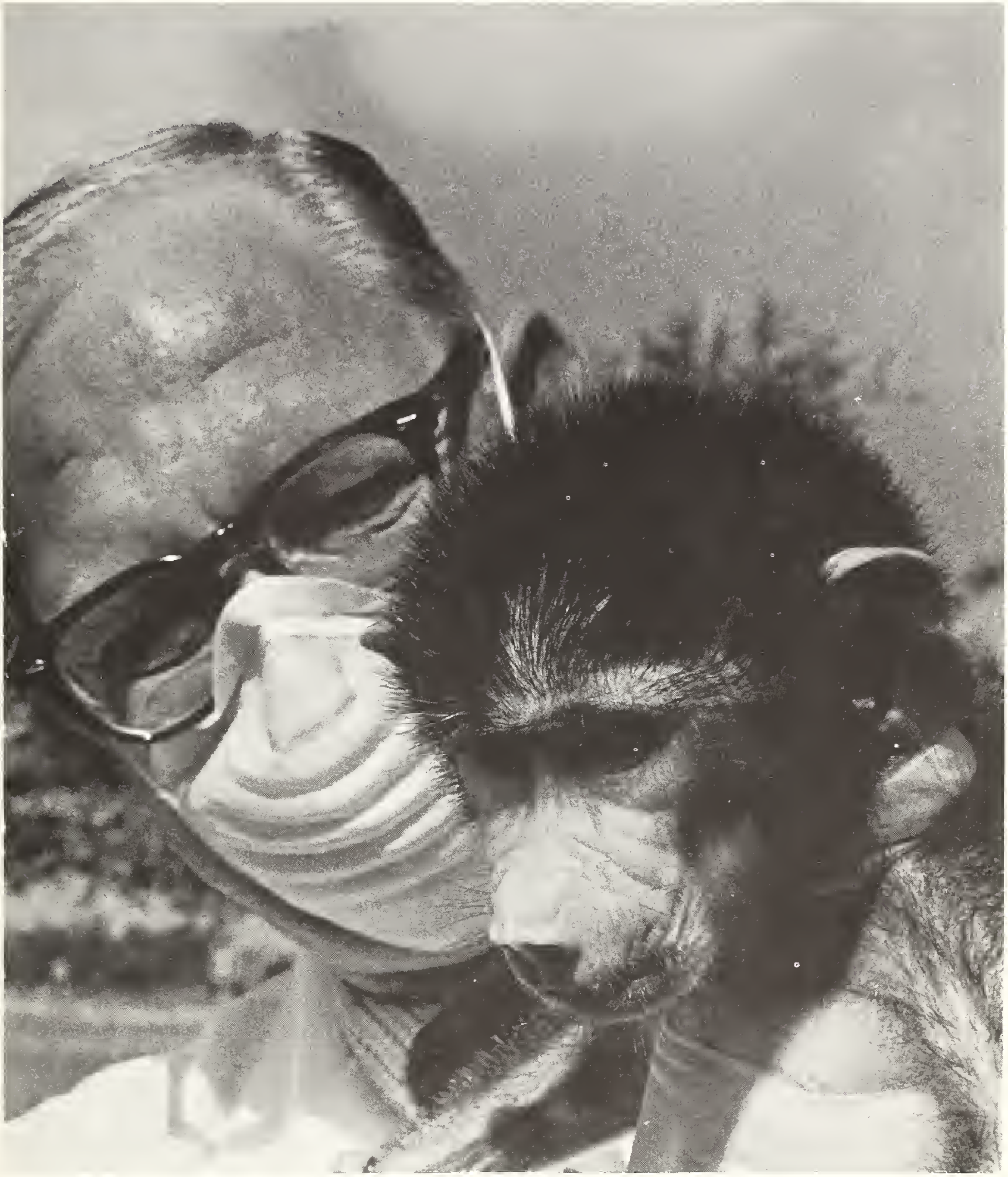
EMBRYO TRANSFER (CONT'D)



The normal eight-week-old infant baboon produced by embryo transfer techniques is held by Dr. Duane C. Kraemer, principal investigator. The successful embryo transfer process was conducted at the Southwest Foundation for Research and Education, San Antonio, under a grant by the National Institutes of Health's Division of Research Resources.

(NIH Photo #1504)

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Research Advances

INTERFERON INDUCER PLUS VACCINE PROTECTS ANIMALS AGAINST RABIES

National Institute of Allergy and Infectious Diseases (NIAID) contractors at the University of Utah have found that, in mice, use of an interferon inducer (poly I.poly C) in conjunction with any one of three rabies vaccines results in a significant reduction in deaths from the disease. The new findings, as well as data obtained by other investigators, indicate that the mechanism of action of the combined effect may be the induction of local interferon which prolongs the incubation period and enhances the immune response.

The NIAID contractors, Drs. Maurice W. Harmon and Burton Janis, suggest, therefore, that consideration should be given to the use of an interferon inducer as an adjunct to vaccination in humans following exposure to rabies.

Rabies is one of the few diseases in man in which vaccines are used following exposure. This is possible due to the relatively long incubation period of the virus. However, this form of therapy is not always successful and is associated with many side effects.

One approach to improvement of rabies vaccines has been the development of tissue-culture-derived virus for vaccine production. Another has been demonstration of protection, in animals, of the interferon inducer, poly I.poly C. The present investigators used a murine model of human street rabies virus infection to evaluate the efficacy of poly I.poly C., of three rabies vaccines, and of combinations of these modes of therapy administered after exposure.

The three inactivated rabies virus vaccines employed in these experiments

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were developed for use in humans: the WI-38; a subviral particle vaccine; and the commonly used duck embryo vaccine.

The investigators found an average mortality rate of 61 percent in control animals given no therapy following exposure to rabies virus, and a similar average mortality rate (62 percent) in vaccine-treated mice. Poly I.poly C, when injected alone into the same site as the challenge virus, reduced the mortality rate to 36 percent.

The most effective therapy, however, was a combination of vaccine and poly I.poly C administration. This treatment resulted in an average mortality rate of 13 percent. Duck embryo vaccine, in conjunction with poly I.poly C, proved to be the most effective, reducing the mortality rate to only eight percent.

Two other rabies vaccines have been shown to be effective in animals when used as the sole means of therapy. These experimental vaccines are unusual in that they themselves induce interferon. Data from the University of Utah investigations confirm the essential role of interferon in protection following rabies exposure since ineffective, non-interferon-inducing vaccines became highly effective when augmented with an interferon inducer.

Drs. Harmon and Janis reported their work in the September 1975 issue of the *Journal of Infectious Diseases*.

#

FLUORIDE SUPPLEMENTS ON CHILDREN'S TEETH STUDIED

For ten years National Institute of Dental Research-supported scientists studied four groups of children, 1,500 in all, living in two non-fluoridated areas (Oneida, New York, and just outside Kalamazoo, Michigan) in order to compare the effects of fluoride supplements, started either at birth or at age four, on the health of their teeth.

Children who received no fluoride served as controls. Other children who received no fluoride supplements but lived for the same period in Kalamazoo proper which has fluoridated water were also compared.

The investigators recorded the amount of new decay in both primary and permanent teeth, the percentage of children with no decay, and also the prevalence of decay in six-year molars.

The scientists report that children with the lowest rates of decay were those who received fluoride from infancy either in the drinking water or in supplements. They note that breast-fed infants receive very little fluoride regardless of the water their mothers drink because human milk lacks this protective substance.

Children who began fluoride supplements at age four showed little difference in decayed *primary* teeth from those who got no supplementary fluoride because by that time the enamel on the first set had already formed. Although their deciduous teeth gained no additional protection, their *permanent* teeth were protected approximately as well as those of children who drank fluoridated water from birth.

Findings in both groups receiving supplements, at birth and at age

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four, were quite similar. The survey of permanent teeth present at ages seven to ten showed that children given fluoride supplements from birth in the area outside of Kalamazoo had the largest percentage of sound teeth and the lowest average number of new decayed and filled teeth. In contrast, children in the control group without any fluoride had only 29.6 percent sound teeth and the average number of new decayed and filled teeth was 1.57. The percentage of sound permanent teeth for children given fluoride supplements from age four and for those drinking fluoridated water from birth were similar (41.9 and 43.4 percent respectively).

The six year molars were studied because they are the first permanent molars to appear, usually the first to be lost because of decay, and the most important for good adult occlusion. Because the outermost layer of enamel forms on these teeth about age four just before eruption, it seemed possible that fluoride supplements begun at age four might benefit them. However, significant caries prevention in six-year molars occurred only when the supplements began at birth.

Preliminary fluoride balance studies of children aged one to four indicated that 30 percent less fluoride was excreted in urine when a single dose of fluoride was consumed with a vitamin supplement than when taken alone. Therefore, all the children in this study were given vitamins to avoid variations which might arise when pediatricians prescribed vitamins for some and not for others. (It is known that fluoride supplements without vitamins are also beneficial.)

(more)

FLUORIDE TREATMENT (CONT'D)

The investigators urge physicians to be aware of the value of prescribing fluoride from infancy (1) in non-fluoride areas and (2) for breast-fed babies regardless of the local water content. Dentists rarely see children before age three, hence cannot usually help prevent tooth decay in these young children during the critical time of tooth calcification.

These findings were reported in the *American Journal of Diseases of Children*, July 1975, by Frederick J. Margolis, M.D., of Wayne State University School of Medicine, Detroit, Michigan; Howard Mehaffey, D.D.S., Dental Division, State Department of Health, Lansing, Michigan; Ernest Freshman, M.D.; John C. Macauley, M.D., in private practice in Oneida; and Harold R. Reames, M.D., in private practice in Kalamazoo.

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Research Advances

NIAID GRANTEES DEVELOP POTENTIAL MODEL FOR STUDY OF PSORIASIS

Grafts of skin from psoriasis patients can be successfully maintained in "nude" mice, according to National Institute of Allergy and Infectious Diseases grantees at the University of Utah College of Medicine, Salt Lake City. This transplantation procedure potentially represents the first useful method whereby the study of psoriasis -- a chronic skin disease -- can be carried out in a nonhuman, living system. Lack of such an animal model has severely hampered research on how the disease develops and how it might be effectively treated.

"Nude" mice are an inbred strain of laboratory animals, born without thymuses. They are thus unable to mount a thymus-dependent immune response, such as that resulting in the rejection of foreign grafts.

Previous reports of the long-term maintenance of normal human skin transplants on "nude" mice prompted Drs. C.G. Krueger and Dean D. Manning, and two medical students -- James Malouf and Bruce Ogden -- to investigate the possibility that psoriatic skin could also be transplanted in these experimental animals. In their pilot study, the Utah investigators experienced technical problems related to thickness of the grafts and positioning them securely on the animals. With the development of better techniques, however, the scientists were able to continue with a study of both involved and noninvolved skin taken from three psoriasis patients.

Of 11 mice receiving donor grafts, ten surviving at least four weeks had successful grafts. Biopsies of the grafts taken every two weeks showed

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that all the animals, on at least two occasions, had graft skin thickening typical of psoriasis. However, an excess of the chemical glycogen, characteristic of psoriasis, was not consistently present, indicating, perhaps, that necessary host factors are not always present in the "nude" mice. These animals are known to develop a wasting syndrome at about three to four months of age -- a general state of nutritive deficiency which could be a factor in an animal's not supporting a psoriatic graft fully typical of the disease.

A report of this research appeared in the May 1975 issue of the *Journal*

This photograph shows a "nude" mouse. (NIH Photo #1505)

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NEWS & FEATURES From NIH

December 10, 1975

Photo Feature

ATHEROSCLEROSIS IN MONKEYS IS REVERSED WITH NEW DRUG

Atherosclerosis (hardening of the arteries) in monkeys can be dramatically reversed with a drug, cholestyramine, now used for other medical purposes, a University of Chicago research team has demonstrated.

Monkeys are commonly used as models for humans in atherosclerosis experiments.

The National Heart and Lung Institute (NHLI) has initiated a test of the drug in a large network of lipid research clinics. The study will utilize human subjects judged at risk for future heart attacks.

Cholestyramine is now used to remove cholesterol-derived bile salts and acids from the gastro-intestinal tract of gallstone victims.

Dr. Wissler, Director of the Specialized Center of Research (SCOR) in Atherosclerosis at the University of Chicago, described the research in a talk at the 48th Scientific Session of the American Heart Association in Anaheim, California, November 17, 1975.

The research was performed under a grant from NHLI to the SCOR unit at the University and with financial support from the University's Louis Block Fund.

The fatty contents of atherosclerotic deposits in the aorta, the principal artery leading from the heart, were reduced by about five-sixths on a low-fat, low cholesterol diet plus cholestyramine in a two-year experiment, Dr. Wissler reported.

Blood cholesterol in the monkeys and the area of fatty plaques in the

(more)

aorta were also both reduced by five-sixths with a combined diet plus cholestyramine therapy.

Lesser improvement was found in monkeys fed the cholestyramine plus a high-fat, high-cholesterol diet and in those fed only a low-fat, low-cholesterol diet.

Cholestyramine resembles a bulk laxative in appearance and dosage. It binds chemically to cholesterol-derived bile salts and acids, which are then excreted from the body.

Otherwise, said Dr. Wissler, the cholesterol by-products would be recycled through the body and provide the materials for more body-synthesized cholesterol.

Co-authors of the paper were Dr. Dragoslava Vesselinovitch, Research Associate (Assistant Professor) in Pathology, Dr. Jayme Borensztajn, Associate Professor in Pathology and in the College, and Randolph Hughes, Chief Technician in Pathology.

Cholestyramine is a resin, sold under various trade names by pharmaceutical houses. It is commonly prescribed to reduce itching caused by increased bile acids in the blood and tissues.

In chemical structure, it is a large indigestible molecule unable to pass through the intestine walls.

Normally, the human body makes a minimal amount of cholesterol and the amount of cholesterol circulating in the blood stream cannot be reduced to less than 130 to 140 mg. per 100 milliliters (130-140mg) percent.

(more)

ATHEROSCLEROSIS (CONT'D)

If the cholesterol circulating in the blood is reduced to a minimum, said Dr. Wissler in an interview, the body will withdraw needed cholesterol from internal cholesterol pools, such as atherosclerotic plaques in the arteries.

Cholestyramine was tested at the University of Chicago on human beings several years ago by a group led by Dr. Richard J. Jones, Director of the University's Coronary Drug Project. He reported that so-called low-density lipoproteins (cholesterol-and protein-containing macromolecules) were reduced in the subjects' blood stream.

Here is a description of the research reported by Dr. Wissler November 17:

Twenty-four monkeys were fed a high-fat, high-cholesterol diet that induced severe fatty-type atherosclerosis within one year. From the eighth to the twelfth month all 24 animals were also fed radioactive tritium-labeled cholesterol, enabling the University of Chicago group to measure the amount of cholesterol in plaques in the aortas of the various test groups at autopsy. Five of the monkeys were autopsied at the end of 12 months to establish the typical extent and location of atherosclerotic lesions at the end of one year. The remaining animals were divided into four groups, of which one continued for another 12 months on the high-fat, high-cholesterol diet, one was treated with a low-fat, cholesterol-free diet, one with the low-fat, low-cholesterol diet plus cholestyramine, and one with the high-fat, high-cholesterol diet plus cholestyramine. The remaining monkeys were autopsied at 24 months.

This is the first time cholestyramine has been used to reverse advanced

(more)

ATHEROSCLEROSIS (CONT'D)

fatty atherosclerotic plaques in the aortas and coronary arteries of experimental animals.

The initial diet during the first 12 months was monkey chow plus a large amount of added cholesterol, coconut oil and butter oil, high in calories. The therapeutic, low-fat diet contained a small amount of corn oil in place of the coconut oil and butter oil. It contained little cholesterol.

The most definite evidence of regression was seen in the group treated with cholestyramine plus the low-fat, low-cholesterol ration. "The amount of regression was considerably more than that produced by the therapeutic diet alone," commented Dr. Wissler.

The group of monkeys treated with cholestyramine alone while continuing on the high-fat, high-cholesterol diet also showed some regression of their aortic disease, as indicated by anatomical tissue and chemical evidence.

Analysis at autopsy of the tritium-labeled cholesterol in the aortic lesions at autopsy indicated that cholestyramine therapy and the low-fat, low-cholesterol diet caused a rather remarkable decrease in both free cholesterol and cholesterol compounds in the lesions, and that in both the free and compound form most of the cholesterol in the lesions could be readily removed.

Dr. Wissler cautioned that the results apply only to fatty-type arterial plaques produced in a relatively short time by a very severe diet. Other uncompleted research is being performed at the University of Chicago on the non-fatty, scarred (collagenous) portions of plaques typical of longer-term

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atherosclerosis, he said. The research does not necessarily apply to older, calcified plaques.

Cholestyramine is sold as a white, tasteless powder. It is usually taken in tablespoon portions in a fruit juice several times a day. It must be used with Vitamin K to counteract an increased tendency to hemorrhage that it may induce.

Some human patients experience constipation, abdominal discomfort, and loss of appetite with its use, but Dr. Wissler did not observe these effects with his experimental monkeys.

Here is Dr. Robert W. Wissler of the University of Chicago. (NIH Photo #1506)

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News Feature

LAETRILE FAILS NCI ANTI-TUMOR TESTING

The National Cancer Institute (NCI) has conducted several series of tests of Laetrile in the animal tumor systems used to screen drugs for anticancer activity. Laetrile is variously described as a form of Amygdalin, a nitriloside, Vitamin B_{17}, or 1-mandelo-nitrile-beta-glucuronide.

Amygdalin is a cyanogenic glucoside that occurs in many plants. Supporters of the drug have used the names Laetrile and Amygdalin synonymously. The compound actually used in all tests at NCI and elsewhere (including clinical studies) has been Amygdalin. The compound was tested alone or in combination with an enzyme, beta-glucosidase. In each of the tests, summarized here, the compound failed to produce a reproducible antitumor effect.

*1957: Amygdalin was tested with three transplanted mouse tumor systems used at the time by the NCI Cancer Chemotherapy National Service Center (CCNSC) to screen compounds for anticancer activity. Amygdalin produced no significant inhibition or growth of the carcinoma 775 or sarcoma 180 tumors, and produced no significant increase in the lifespan of mice with leukemia L1210 tumors.

*1960: Material from a different source was tested against the same three mouse tumors. The compound failed to show antitumor activity.

*1969: Amygdalin was tested alone and in combination with beta-glucosidase against leukemia L1210 in mice. Amygdalin was inactive against the tumor, alone and in combination with the enzyme. Toxic side effects increased when the drug and enzyme were given together.

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*1973: Amygdalin was tested alone and in combination with beta-glucosidase against the Walker 256 carcinoma in rats and against the following four-tumor mouse screen currently in use by NCI: leukemia L1210, lymphoid leukemia P388, B16 melanoma, and Lewis lung carcinoma. Amygdalin was completely inactive against the four tumors, alone or in combination with the enzyme.

*1975: Amygdalin was tested alone and in combination with beta-glucosidase against three transplanted mouse tumors; lymphoid leukemia P388, Lewis lung carcinoma, and Ridgway osteogenic sarcoma. In these tests, Amygdalin had no antitumor activity.

Tests of Amygdalin are continuing at the Memorial Sloan-Kettering Cancer Center, New York City, with spontaneous, naturally-occurring mammary (breast) tumors in two strains of mice: Swiss and CD8F1 hybrid. To date, Amygdalin has shown no reproducible effect on either growth of the original tumors or development of subsequent metastases. Scientists at the Memorial Sloan-Kettering Cancer Center are also testing the effects of Amygdalin against a spontaneous, naturally-occurring leukemia in AKR mice.

NCI is conducting additional tests of Amygdalin against a metastatic mouse tumor, the Lewis lung carcinoma. The current tests are directed toward assessing the effect of Amygdalin on development of metastases from the tumor. Previous tests showed conclusively that Amygdalin did not inhibit growth of the primary tumor, nor did it reproducibly increase the lifespan of the mice.

Chemically, Amygdalin is a derivative of a molecule called mandelo-

(more)

LAETRILE (CONT'D)

nitrile. Specifically, it is mandelonitrile-beta-gentiobioside, in which mandelonitrile is linked with a chain of two glucose units. The enzyme beta-glucosidase, used in some of the tests, can break the link between mandelonitrile and the one or more sugar derivatives. Mandelonitrile may decompose further, releasing highly toxic cyanide.

Ernst T. Krebs, Jr., who claimed the synthesis of Laetrile in 1952, proposed that the compound acted through the release of cyanide in cancer cells. He suggested that normal cells contain an enzyme called rhodanese that detoxifies cyanide by coverting it to thiocyanate.

Past NCI tests of Laetrile in many rodent tumor systems have failed to produce evidence of anticancer activity. Because there is no basis for predicting that Amygdalin might act against cancer in humans, NCI does not intend to test Amygdalin in cancer patients. Nevertheless, NCI is committed to pursuing any evidence that might provide a basis for clinical trials with cancer patients.

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Photo Feature

NEW MEDICINAL AGENTS TO BE STUDIED AT UNIVERSITY OF IOWA

A five-year $800,000 program-project grant to the University of Iowa will support an interdisciplinary effort directed toward the synthesis and evaluation of new medicinal agents.

Dr. John P. Long, professor and head of pharmacology in the U of I College of Medicine, is principal investigator in the program supported by the National Institute of General Medical Sciences. Dr. Joseph G. Cannon, professor and assistant dean for graduate studies and research, and Dr. C.F. Barfknecht, professor and head of medicinal chemistry and natural products in the College of Pharmacy, are co-investigators.

New drugs, some developed at the U of I, will be evaluated in animal studies in the Department of Pharmacology. Results from the biological studies will be used in modifying the chemical composition or the molecular structure of the drugs for further testing.

In a series of projects, the researchers will study drugs that have effects on Parkinson's disease, blood pressure, and the release of the hormone, prolactin.

"The problem with most of our drugs today is that they lack specificity of action," Dr. Cannon noted. "The drugs do not do just one thing, they affect other areas. For example, the anti-Parkinson drugs decrease the symptoms (tremor, rigidity), but in some persons they also trigger a severe emetic, or vomiting, effect."

The site of the reaction between the drug molecule and the nerve cell must be investigated so a closer "fit" can be made, the researchers note.

(more)

MEDICINAL AGENTS (CONT'D)

"Right now we have a situation in which we are hitting two keys on the piano: reduction of symptoms and increase in vomiting," Dr. Barfknecht explained. "We want to design a drug that will have a blocking effect on that second key."

In addition, research will center on inhibitors of the sympathetic nervous system, studying drugs that have effects on the cardiovascular system and the blood circulation of the kidney.

Another area of study will be research on drugs which stimulate specific portions of the sumpathetic nervous system, for example, areas active as a person enters a state of "shock" with decreased heart function and lowered blood pressure.

The researchers are also investigating drugs which inhibit the release of prolactin, and important hormone whose role in disease is not completely understood.

While studying specific drugs, the program also is aimed at defining more closely how the receiving places on the cell wall are organized so a more general understanding of drug action is achieved.

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MEDICINAL AGENTS (CONT'D)

Two pigeons, Henry (left) and Maude, have been helping some University of Iowa researchers find out how drugs work. A grant to the University of Iowa from the National Institute of General Medical Sciences will aid in studying medicinal agents which affect Parkinson's disease, high blood pressure, and "shock". Participating in the project are (from left) Dr. Joseph G. Cannon, Dr. C.F. Barfknecht, and Dr. John P. Long, principal investigator. When Henry and Maude have finished their duties in the lab in another six months, they will be set free to fly over Iowa City rooftops. (NIH Photo #1507)

News Feature

CAUSE IS FOUND FOR SOME NONGONOCOCCAL URETHRITIS

In a study evaluating the causes of nongonococcal urethritis (NGU), found to be common in sexually active men, investigators supported by National Institute of Allergy and Infectious Diseases and others reported that about half of the cases were caused by *Chlamydia trachomatis*. However, *Herpes virus hominis*, cytomegalovirus, T-mycoplasma, *Mycoplasma hominis*, *Trichomonas vaginalis*, and other bacteria, were not factors in infections of the group studied.

The scientists, Drs. King K. Holmes, H. Hunter Handsfield, San Pin Wang, Berttina B. Wentworth, Marvin Turck, Joanne B. Anderson, and E. Russell Anderson, are from the University of Washington and the USPHS Hospital and Harborview Medical Center in Seattle. Their findings were published in the June 5, 1975, issue of the *New England Journal of Medicine*.

NGU usually is found to occur more frequently among sexually active men than urethritis caused by gonococcus, especially among whites and the more affluent. Until now, control of NGU has been limited by lack of data pertaining to its cause. It is important to differentiate NGU from gonococcal infection since NGU does not respond to penicillin as does gonococcal infection. Several organisms, including various bacteria and viruses, have been implicated in NGU, however, no study has evaluated these agents simultaneously.

Dr. Holmes and his colleagues surveyed three groups of men -- 118 with NGU, 58 without overt urethritis, and 69 with gonorrhea. *C. trachomatis* was isolated from 42 percent of the men with NGU, seven percent of the men without

(more)

NONGONOCOCCAL URETHRITIS (CONT'D)

urethritis, and 19 percent with gonorrhea. The same organism was also responsible for all of the 11 cases of postgonococcal urethritis that developed during this study. Other organisms, including bacteria and viruses that are sometimes implicated in urethritis, were not significant in this group. The cause of non-chlamydial NGU, therefore, is still obscure.

C. trachomatis was recovered from 15 sexual partners of 22 patients with NGU caused by the organism. Since the organism apparently is sexually transmitted, the investigators advise that both partners be treated with tetracycline.

In 1974 NIAID established a grant-supported Venereal Disease Center at the University of Washington and under the direction of Dr. Holmes.

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Photo Feature

NEW ENVIRONMENTAL HEALTH SCIENCES CENTER ESTABLISHED

The National Institute of Environmental Health Sciences (NIEHS) has awarded a grant of approximately $3.2 million to the University of Rochester, Rochester, New York, for establishment of an Environmental Health Sciences Center.

The new Center will be headed by Dr. Thomas W. Clarkson, Professor in the School of Medicine at Rochester. He has been an individual grantee of NIEHS and has done important research on trace metals--particularly mercury--as environmental health hazards for several years. Center personnel will study a wide spectrum of trace metal contaminants and combinations of contaminants that may have harmful effects on human health.

They will concentrate on the biological consequences of exposure to low-level concentrations of trace contaminants, particularly the low amounts present in the average urban environment. Human consequences of such exposure are largely unknown.

According to Dr. David P. Rall, Director of NIEHS, the importance of trace substances in our environment, particularly in food and water, came to the fore at the turn of the century. In recent years there has been a great surge of interest in such trace metals as mercury, lead, and cadmium; and important discoveries have been made.

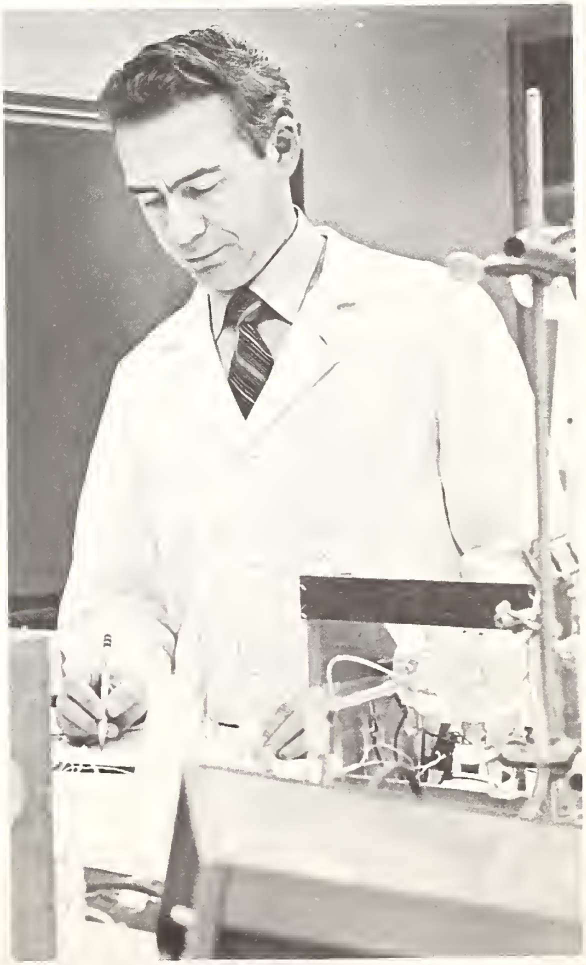
Some environmentally-related health hazards have been reduced or eliminated due to these discoveries; others, however, have now become the focus of interest. During the past few decades, for example, effective health regulations and environmental control procedures have largely eliminated

(more)

ENVIRONMENTAL CENTER (CONT'D)

lead intoxication as a cause of industrial illness in the United States. In recent years, however, interest in the deleterious effects of lead has shifted from the industrial field to that of potential hazards to the community at large.

"The University of Rochester group has already developed much fundamental knowledge needed to protect man against hazardous contaminants in the environment," Dr. Rall commented. "And the interdisciplinary approach used by this group is vital in the area of trace contaminants research. We expect much new valuable research from them, and it is for this reason that the University of Rochester has been chosen as the seventh Center supported by NIEHS for research on multi-faceted environmental health problems."



Thomas W. Clarkson, Ph.D., professor at the University of Rochester School of Medicine and Dentistry, checks the levels of total organic and inorganic mercury in samples of hair taken from an individual who may have been exposed to the metal. (NIH Photo #1508)

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News Feature

NIH TO STUDY "PEER REVIEW"

A comprehensive study of the procedures generally known as "peer review" is under way at the National Institutes of Health. Ruth L. Kirschstein, M.D., Director of the National Institute of General Medical Sciences, is Chairperson of the Grants Peer Review Study Team. The Study Team is actively soliciting written comments and suggestions relative to the peer review system from all interested parties. These should be sent to: Dr. Mathilde Solowey, Executive Secretary, NIH Grants Peer Review Study Team, Building 31, Room 4A35, NIH, Bethesda, Maryland 20014.

In addition, hearings on the peer review system will be held during February 1976 as follows: February 12, in Chicago, 219 S. Dearborn Street, Room. 204A; February 19, in San Francisco, 555 Battery Street, Room 503; February 26, in Bethesda, NIH Building 1, Third Floor, Wilson Hall. Hearings will last all day.

General topics on which information is being sought are: the adequacy and effectiveness of the present system, including the initial scientific review; Council review and the priority rating system; the impact of the Privacy Act of 1974, the Freedom of Information Act, and the Federal Advisory Committee act; and recommendations as to how the present system can be improved.

Persons wishing to attend the hearings or present statements should contact Dr. Solowey.

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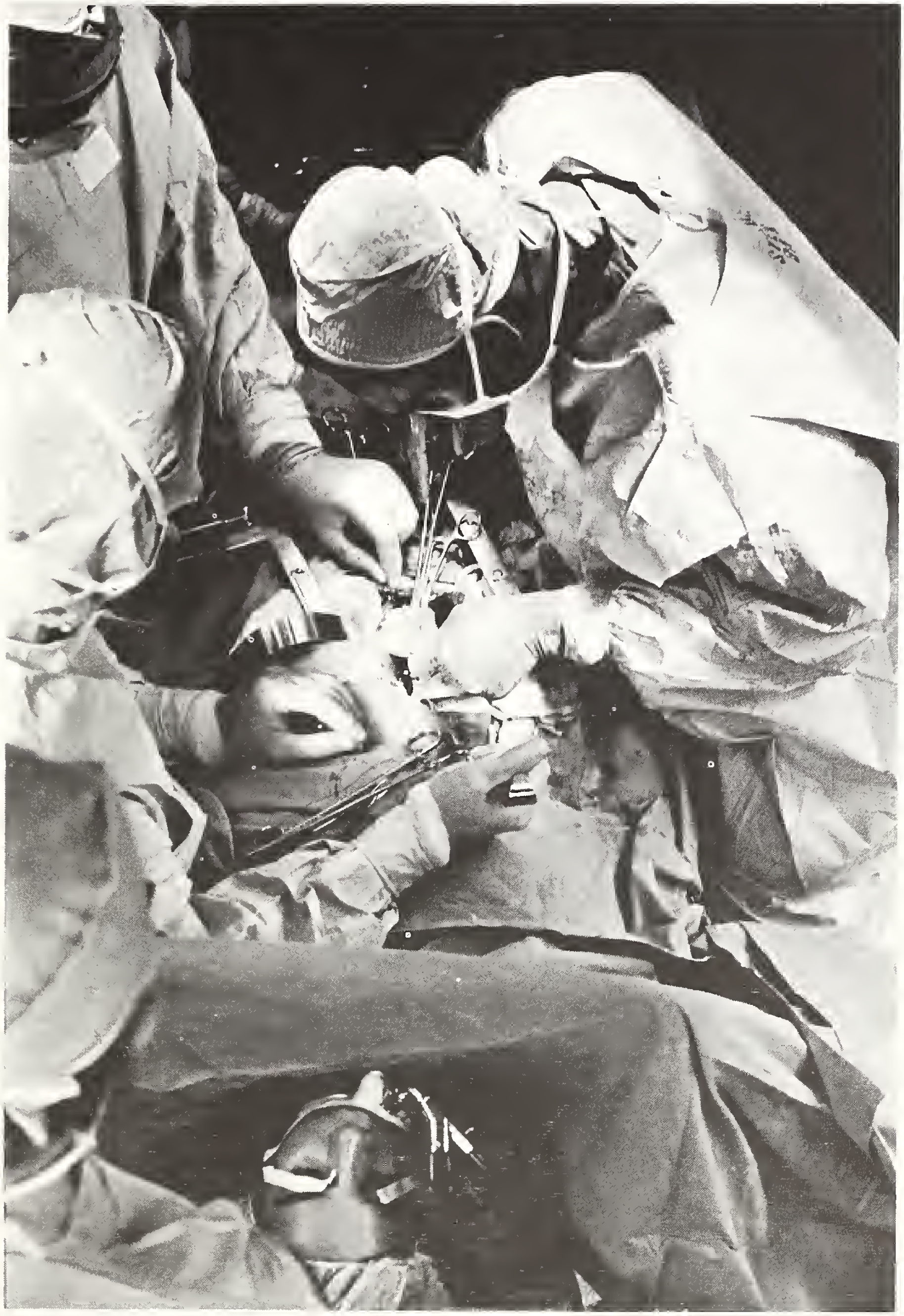
Research Illustrated

TWO OUTSTANDING MEDICAL SCIENTISTS SHOWN AT WORK



Dr. Samuel L. Kountz, Chairman of the Department of Surgery at Downstate Medical Center, is shown performing one of the kidney transplant operations for which he is renowned. His research work is supported in part by the National Institutes of Health. (NIH Photo #1509)

(more)

RESEARCH ILLUSTRATED (Cont'd)

Dr. H. Gobind Khorana is shown working in one of his laboratories at the Massachusetts Institute of Technology. He is noted for his work to synthesize an artificial gene. Some of his laboratory research is funded by the National Institutes of Health. (NIH Photo #1510)

Disease Profile

CEREBRAL PALSY IS THE RESULT OF DAMAGE TO MOTOR CONTROL CENTERS

Cerebral palsy is a common handicapping condition, not due to progressive disease. It is characterized primarily by spastic paralysis or impairment of control or coordination over voluntary muscles. Manifestations may change over the lifespan of the individual. It is often accompanied by mental retardation, seizures, and disorders of vision and communication.

Cerebral palsy may be either congenital or acquired, but it is always the result of damage to the brain's motor control centers. It has many known or suspected causes, and there is no single effective preventive measure. Although a cure is not available for the condition, the afflicted person can be helped to minimize the effects of cerebral palsy and to compensate for developmental delays.

The National Institute of Neurological and Communicative Disorders and Stroke reports that about 750,000 Americans have cerebral palsy. About 15,000 babies are born with cerebral palsy each year, or one newborn in every 200 live births.

The various syndromes known as cerebral palsy are classified according to several predominant clinical manifestations. Spastic Cerebral Palsy is characterized by increased muscle tension and exaggerated reflex activity in an arm and a leg on the same side (hemiplegia) or arms and legs on both sides (tetraplegia or quadriplegia). In some cases, the lower limbs may be more involved than the upper limbs (diplegia) or both legs may be involved with complete sparing of the arms (paraplegia). In rare cases, only one limb (monoplegia) or three limbs (triplegia) are involved. Dyskinetic Cerebral Palsy is characterized by uncontrolled

(more)

and purposeless movements which disappear during sleep. The most common type is athetosis involving usually all four extremities, but also the face, neck, and, to a lesser degree, the trunk. Ataxic Cerebral Palsy is characterized by an inability to coordinate voluntary muscular movements.

The manifestations of more than one type of cerebral palsy may occur in some children. Also children with cerebral palsy may have associated defects which in some instances may be more disabling than the motor disability itself. The most common of these are seizure disorders and mental retardation. Cerebral palsy is often accompanied by speech disorders, including different degrees and expressions of aphasia (total or partial loss of the power to use or understand words) and articulatory disturbances. Faulty hearing, visual defects, perceptual and conceptual difficulties, and personality disorders are other problems sometimes associated with cerebral palsy.

Because cerebral palsy is such a complex condition, it can be most effectively managed through the team approach. Management varies with the child's age, the type and severity of involvement, the presence or absence of seizures, and the level of intellectual capability. All of these factors require skillful management by a team of physicians, therapists, social workers, educators, and psychologists. Recent focus on the whole child and his family, including social and educational factors, has helped family adjustment and the child's education and future occupation.

Spasticity is the dominant motor handicap in most cases of cerebral palsy. It can be treated symptomatically by physical and occupational therapy, and with orthopedic and neurological techniques. The potential

(more)

of certain medications for treatment is under study.

In order to determine the correct therapeutic approach, it is necessary to observe carefully what the patient can do and evaluate the degree of spasticity.

Drugs such as L-Dopa, used for many years for the treatment of Parkinson's disease, and sodium dantrolene are being evaluated to determine whether or not they might be effective in controlling muscle tension. The use of surgery, pneumatic braces, and injections of alcohol are still being appraised.

Although much is yet unknown about the causes and management of cerebral palsy, research progress has been steady and occasionally dramatic. Scientists believe that many birth defects could be prevented by a wider application of this new knowledge. One simple step would be for all women of childbearing age--even young girls--to receive anti-rubella vaccine.

A second step would be for all couples to have their blood analyzed for Rh factor incompatability (a destructive blood disease), and for an Rh-negative mother to be given an Rh vaccine after delivery which will protect future children against Rh-incompatability. Researchers also point out that genetic services now are available in many cities. Some of the centers provide genetic counseling, and others provide prenatal diagnosis of hereditary defects. Good prenatal care is the best protection against non-genetic birth defects, and research findings strongly suggest that the mother-to-be avoid the use of unprescribed drugs and medicines,

(more)

CEREBRAL PALSY (CONT'D)

and follow her physician's instructions regarding those prescribed. Research also indicates that the pregnant woman should avoid persons with infectious diseases and give particular attention to proper nutrition.

Research has made all of these preventive measures available. As more and more people are made aware of them and their use becomes more widespread, it is anticipated that brain damage which results in cerebral palsy can be significantly reduced.

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